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UNVEILING THE GENETIC BLUEPRINT: DIAGNOSING MICPCH IN A MALE NEONATE THROUGH EXOME SEQUENCING

Neonatology

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ABSTRACT

MICPCH is an extremely rare neurodevelopmental disorder, particularly in males. We present a case of a twenty-five-day-old male neonate with refractory seizures and dysmorphic features, diagnosed with cerebellar hypoplasia. Whole exome sequencing identified a pathogenic CASK gene mutation. This case highlights the role of genetic testing in early diagnosis and management of unexplained neurodevelopmental disorders in neonates.

KEYWORDS

Next Generation Sequencing; Refractory Seizure; Neonatal Seizures

INTRODUCTION

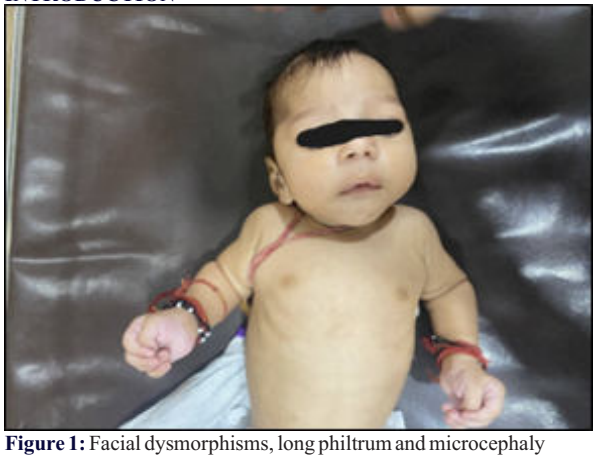


Figure 1: Facial dysmorphisms, long philtrum and microcephaly

Cerebellar hypoplasia is a neurological condition characterized by underdevelopment of the cerebellum, leading to a range of motor and cognitive impairments. Genetic factors play a significant role in the etiology of cerebellar hypoplasia.[1]

Figure 2: Already Set In Rigidity And Scissoring At 4 Months Age

Microcephaly is defined as a head circumference more than 3 standard deviations (SD) smaller than the typical value in babies of the same sex and age and can result in asymptomatic to severe developmental delays and refractory seizures. Intellectual developmental disorder with microcephaly and pontine and cerebellar hypoplasia (MICPCH) is an X-linked disorder predominantly affecting females with only a few reported cases in males.

Calcium/calmodulin-dependent serine protein kinase (CASK)-associated MICPCH is extremely rare, and more than 50 females and a few males with MICPCH have been described.

While cases have been reported in female infants and toddlers, reports in neonates, particularly males, remain extremely rare.

Our case highlights the importance of using clinical and radiologic phenotype to guide genetic investigation, especially when the antenatal course and immediate natal history is not significant.

CASE PRESENTATION

A 37 weeks term live male infant was delivered via caesarian section at a local hospital. There were no remarkable complications during pregnancy. Infant weighed 2500 g at birth (50th percentile), length of 48 cm (50th percentile).

The infant presented with refractory seizures, requiring Phenobarbital and Levetiracetam, later determined to be dyskinetic rather than epileptic as EEG showed no epileptic activity even after tapering and stopping anti-epileptic medications.

He was found to have dysmorphic features on examination, namely microcephaly with prominent occiput, low set ears and long philtrum (Figures 1 and 2).

Family Pedigree Chart (Figure 3)

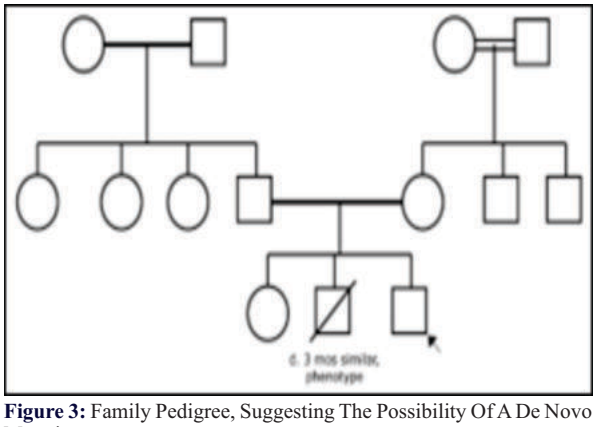


Figure 3: Family Pedigree, Suggesting The Possibility Of A De Novo Mutation

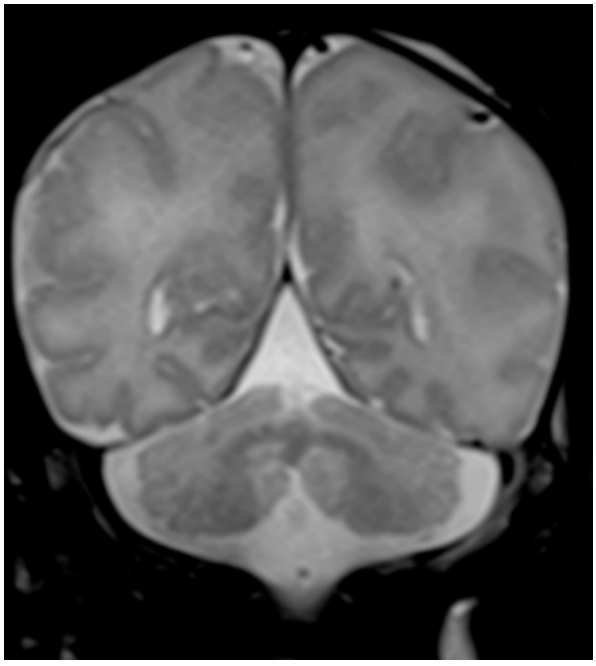


Figure 4: Hypoplastic cerebellum, decreased cortical grey white differentiation

His MRI brain showed severe hypoplastic pons with reduced gyral and sulcal differentiation and hypoplastic corpus callosum (Figures 4 and 5). He was started on Clonazepam as per paediatric neurologist's advice, with which his clonic movements had decreased in frequency.

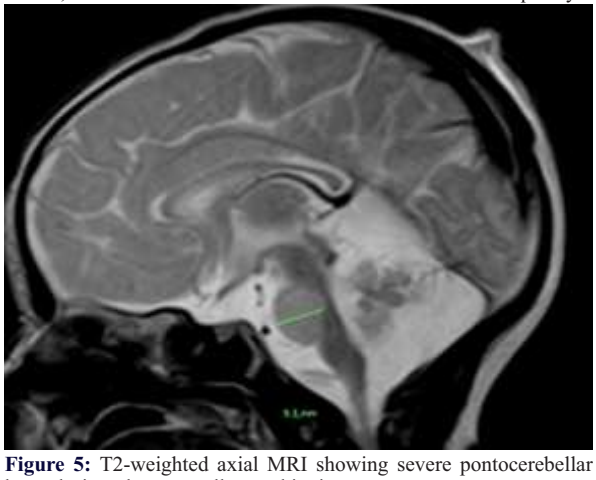


Figure 5: T2-weighted axial MRI showing severe pontocerebellar hypoplasia and corpus callosum thinning

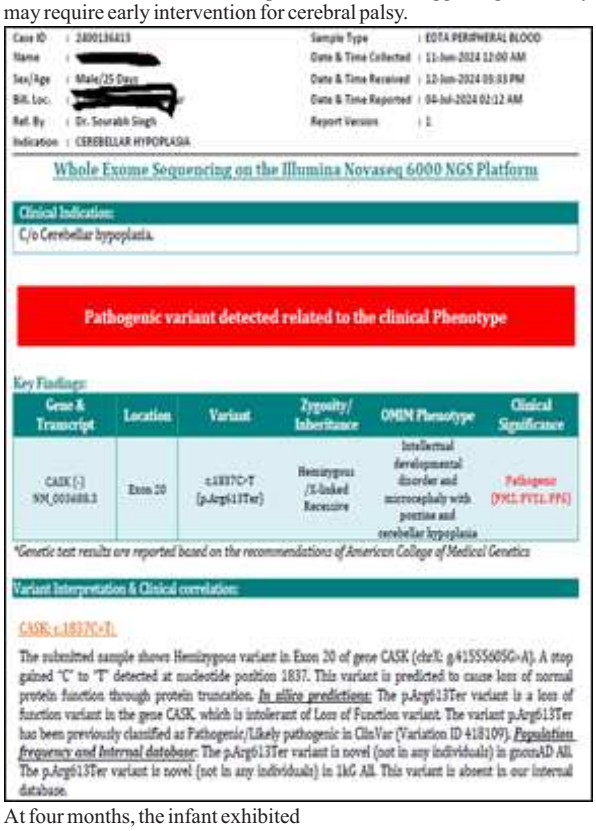
With no clear picture of how to proceed therapeutically or definitive diagnosis, we had sent blood for genetic analysis.

Whole exome sequencing identified a hemizygous pathogenic variant (p.Arg613Ter) in the CASK gene, a known loss-of-function mutation associated with MICPCH, classified as pathogenic in CliniVar (Variation ID 418109) based on ECMG guidelines.

The CASK gene is the causative gene of intellectual developmental disorder and MICPCH (OMIM #300172), which is inherited in an X-linked dominant manner and is characterized by severely impaired intellectual development and varying degrees of pontocerebellar hypoplasia. The patient's features and symptoms were consistent with those of MICPCH. Parents were counselled about the syndrome, disease outcome and long term prognosis as per available published data.

OUTCOME

Baby was discharged on Clonazepam and Levetiracetam. Although parents were scheduled for monthly follow-ups we could only examine the baby four and six months of age, where the HINE examination scores were suboptimal about 52 suggesting that baby may require early intervention for cerebral palsy.



Case ID : 2400136413 | Sample Type : EDTA PERIPHERAL BLOOD
Name : [redacted] | Date & Time Collected : 11-Jun-2024 12:00 AM
Sex/Age : Male/25 Days | Date & Time Received : 12-Jun-2024 05:03 PM
Bill. Loc. : [redacted] | Date & Time Reported : 04-Jul-2024 02:12 AM
Ref. By : Dr. Sourabh Singh | Report Version : 1
Indication : CEREBELLAR HYPOPLASIA

Whole Exome Sequencing on the Illumina Novaseq 6000 NGS Platform

Clinical Indication:
C/o Cerebellar hypoplasia.

Pathogenic variant detected related to the clinical Phenotype

Key Findings:

Gene & Transcript	Location	Variant	Zygosity/ Inheritance	OMIM Phenotype	Clinical Significance
CASK (-) NM_003688.3	Exon 20	c.1837C>T (p.Arg613Ter)	Hemizygous /X-linked Recessive	Intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia	Pathogenic (PVS1, PS3, PM2, PP5)

*Genetic test results are reported based on the recommendations of American College of Medical Genetics

Variant Interpretation & Clinical correlation:

CASK: c.1837C>T:

The submitted sample shows Hemizygous variant in Exon 20 of gene CASK (chrX: g.41555605G>A). A stop gained "C" to "T" detected at nucleotide position 1837. This variant is predicted to cause loss of normal protein function through protein truncation. *In silico predictions:* The p.Arg613Ter variant is a loss of function variant in the gene CASK which is intolerant of Loss of Function variant. The variant p.Arg613Ter has been previously classified as Pathogenic/Likely pathogenic in ClinVar (Variation ID 418109). *Population frequency and Internal database:* The p.Arg613Ter variant is novel (not in any individuals) in gnomAD All. The p.Arg613Ter variant is novel (not in any individuals) in 1kG All. This variant is absent in our internal database.

At four months, the infant exhibited
1. Severe feeding difficulties requiring nasogastric tube feeding
2. Global developmental delay
3. Limb rigidity.
4. Clonic movements had reduced as per parental reports.

DISCUSSION

The CASK gene is located at Xp11.4 and encodes the CASK protein composed of 926 amino acids.[2]

CASK is a synaptic scaffolding protein involved in neuronal migration and synapse formation. Its loss disrupts neural connectivity, leading to microcephaly and cerebellar hypoplasia.

The CASK protein belongs to the membrane-associated guanylate kinase family and involves multiple functional domains, including L27 (LIN-2 and LIN-7 interaction), PDZ (PSD95, Discs-large, ZO-1), SH3 (src homology 3), and additional N-terminal calcium/calmodulin-dependent kinase (CaMK) and C-terminal guanylate kinase (GK) domains.

It is a multiprotein complex assembler in central nervous system synapse that plays a role in gene expression control throughout neural development, protein trafficking, ion channel signaling, and synaptic contact.[3]

CASK regulates mitochondrial respiration and oxidative metabolism, and nutrition and energy deprivation of the rapid growth of brain after birth disproportionately limits the growth of the cerebellum.[4]

Its mutations lead to interference of the neuronal migration and consequent neurodevelopmental disorder.

Some of the reported literature on CASK mutations mention a maternal inheritance, however, in our case, it seems to be a de novo mutation. CASK mutations are usually maternally inherited but can also be de novo.[3]

CASK mutations result in a spectrum of neurodevelopmental disorders, from mild intellectual disability to lethal male phenotypes.[3]

The variant p.Arg613Ter has been previously classified as Pathogenic/Likely pathogenic in ClinVar (Variation ID 418109).

Population frequency and Internal database: The p.Arg613Ter variant is novel (not in any individuals) in gnomAD All.

The p.Arg613Ter variant is novel (not in any individuals) in 1kG All database.

Other pathogenic variants of the same genetic mutation have been found though, although less severe, as the disease is thought to be lethal in males.[3]

Clinical suspicion should be raised in neonates with unexplained developmental delay, microcephaly, and seizures, particularly when perinatal injury and reasonably positive family history has been ruled out.

Differential diagnoses included congenital infections and perinatal hypoxic-ischemic injury. TORCH panel sent was normal. MRI brain did not show features strongly suggestive of HIE.

This case underscores the role of exome sequencing in neonates with unexplained neurodevelopmental abnormalities and highlights the importance of early diagnosis for optimizing management and parental counselling.

Currently, there is no curative treatment for MICPCH. Management is supportive, including seizure control, feeding assistance and physiotherapy to optimize motor function.

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