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A child with Global Developmental Delay and Seizures: Clinical, Neuroimaging, and Genomic Correlation

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Abstract

Global developmental delay (GDD) with early-onset seizures presents a diagnostic challenge, particularly in the absence of clear perinatal insult. Neuroimaging and genomic evaluation aid in differentiating acquired cerebral palsy from genetic neurodevelopmental disorders. We report a one-year-old female child with global developmental delay, seizures, and clinical features suggestive of spastic quadriplegia. MRI brain revealed diffuse cerebral atrophy with delayed myelination, inconsistent with hypoxic-ischemic injury. Whole exome sequencing identified heterozygous variants of uncertain significance in SMARCE1 and NALCN genes. This case highlights the importance of combined clinical, radiological, and genetic assessment in children with developmental encephalopathy.

Introduction

Global developmental delay affects approximately 1–3% of children and is frequently associated with epilepsy. While cerebral palsy is often attributed to perinatal hypoxic injury, an increasing number of children initially labeled as cerebral palsy are later found to have genetic etiologies. Whole exome sequencing (WES) has improved diagnostic yield; however, interpretation of variants of uncertain significance remains challenging. This report emphasizes the role of MRI brain correlation and genomic testing in a child with neurodevelopmental impairment.

Case Presentation

A one-year-old female child presented with delayed developmental milestones and recurrent seizures. She was born to non-consanguineous parents following an uneventful antenatal and perinatal period. There was no history of birth asphyxia, neonatal seizures, central nervous system infections, or significant jaundice. Family history was non-contributory.

Developmental assessment revealed delay across all domains. The child had poor head control, was unable to sit without support, and had limited vocalization. Neurological examination showed increased tone in all four limbs with exaggerated deep tendon reflexes, suggestive of spastic quadriplegia. Seizures were characterized by generalized episodes and were managed with antiepileptic medications.

Based on clinical findings, a diagnosis of global developmental delay with epilepsy, clinically suspected to be quadriplegic cerebral palsy, was considered, and further evaluation was undertaken.

Investigations

MRI Brain

MRI brain demonstrated:

- Diffuse cerebral volume loss with prominence of cortical sulci
- Delayed myelination for age
- Mild ventriculomegaly
- Absence of focal periventricular leukomalacia, intracranial hemorrhage, or cortical malformations

These findings were not classical for hypoxic-ischemic encephalopathy, suggesting a non-acquired, developmental etiology.

Genetic Evaluation

Whole Exome Sequencing (WES) was performed using next-generation sequencing technology, including analysis of single nucleotide variants, insertions/deletions, copy number variations, and mitochondrial DNA variants.

Results:

- No clinically significant copy number variations detected
- No clinically relevant mitochondrial DNA variants detected
- Identified Variants:

Gene	Transcript	Variant	Zygosity	Inheritance	Classification	Associated disorders
SMARCE1	NM_003079.5	c.256G>T (p.Ala86Ser)	Heterozygous	Autosomal dominant	Variant of uncertain significance	Coffin–Siris syndrome 5
NALCN	NM_052867.4	c.4549T>C (p.Tyr1517His)	Heterozygous	Autosomal dominant / recessive	Variant of uncertain significance	Infantile hypotonia with psychomotor retardation

Discussion

The absence of perinatal insult and the presence of non-specific MRI brain abnormalities such as diffuse cerebral atrophy and delayed myelination argue against a diagnosis of acquired cerebral palsy. Such imaging patterns are increasingly recognized in genetic developmental encephalopathies.

Variants in SMARCE1, a gene encoding a chromatin remodeling protein, have been associated with Coffin–Siris syndrome, characterized by developmental delay, hypotonia, and intellectual disability. Similarly, pathogenic variants in NALCN, which encodes a neuronal sodium leak channel, are linked to severe neurodevelopmental disorders with hypotonia, seizures, and abnormal neuroimaging.

Although both variants identified in this child are currently classified as variants of uncertain significance, the overlap between the child's clinical phenotype, MRI brain findings, and known disease associations

supports a likely genetic basis. This case exemplifies the diagnostic complexity posed by VUS findings and highlights the need for clinical correlation, parental segregation studies, and periodic reanalysis of genomic data.

Conclusion

This case underscores the importance of integrating clinical examination, neuroimaging, and genomic testing in children with global developmental delay and epilepsy. MRI brain findings inconsistent with hypoxic injury should prompt consideration of genetic etiologies. While whole exome sequencing did not yield a definitive pathogenic variant, the identified variants of uncertain significance, in conjunction with clinical and radiological features, suggest an underlying genetic neurodevelopmental disorder.

Key Learning Points

- Not all children with spastic quadriplegia have acquired cerebral palsy.
- MRI brain plays a crucial role in identifying genetic "cerebral palsy mimics."
- Variants of uncertain significance require cautious interpretation and long-term follow-up.
- Periodic reanalysis of WES data can improve diagnostic yield over time.