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CASE REPORT

BRD4 GENOTYPE OF CORNELIA DE LANGE SYNDROME RESISTANT TO TYPICAL ANTI-EPILEPTICS

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ABSTRACT

Cornelia de Lange syndrome (CdLS), a rare congenital disorder, is estimated to occur in approximately 1 in 10,000 to 1 in 30,000 live births, and there's no specific data on its incidence in India, but it's believed to be a global condition with no racial predilections. As mild cases of CdLS often are not reported, the incidence and prevalence are probably underestimated. Presently, the estimated incidence in the United States has been reported between 1 per 10000 to 1 per 50000 newborns. The disorder affects males and females equally due to a dominant genetic pattern(1). Epilepsy manifested between age 6 months and 16 years. The majority of patients (64.3%) presented with seizures and interictal EEGs mainly revealed focal epileptic paroxysms involving temporal and parietal areas. The majority of the seizures were controlled by Sodium Valproate monotherapy. Otherwise monotherapy with topiramate, levetiracetam, carbamazepine and oxcarbazepine is also effective in controlling seizures. CdLS is a developmental disorder that affects many parts of the body. The features of this disorder vary widely among affected individuals and range from relatively mild to severe.

There are various genetic variations that contribute to CdLS.

- NIPBL gene (Chromosome 5p13.2) – is the most common cause (60-70%)
- SMC1A gene (X chromosome, Xp11.22) – accounts for 5-10% of cases.
- SMC3 gene (Chromosome 10q25) – A rarer autosomal dominant cause.
- RAD21 gene (Chromosome 8q24.11) – a milder form of CdLS.
- BRD4 gene (Chromosome 19p13.12) – rare contributor to CdLS.

In this particular case we have discussed the presentation, management, investigation, finding, diagnosis of gene mutation BRD4 related CdLS in a girl 5years old.

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INTRODUCTION

Cornelia de Lange syndrome is characterized by developmental delay along with short stature, intellectual disability and abnormalities of bones in the arms, hands, and fingers. Most people with CdLS also have dysmorphism-including synophrys, long eyelashes, low-set ears, dental abnormalities, and a small and upturned nose. Many affected individuals also have features similar to autism spectrum disorder. Additional signs and symptoms include hypertrichosis, microcephaly, cleft palate, hearing loss, heart defects, and eye problems(2). Seizure disorders associated with majority of CdLS patients preferentially with autism spectrum disorder. The diagnosis of CdLS is established in a proband with suggestive clinical features and/or by identification of a heterozygous pathogenic variant in *NIPBL*, *RAD21*, *SMC3*, or *BRD4*, or a homozygous pathogenic variant in *HDAC8* or *SMC1A* by molecular genetic testing. BRD4 is a very rare contributor to CdLS. Aggressive management of gastroesophageal reflux with assessment of potential gastrointestinal malrotation; consideration of fundoplication if reflux is severe. Supplementary formulas and/or gastrostomy tube placement to meet nutritional needs as necessary. Physical, occupational, and speech therapy to optimize psychomotor development and communication skills. Standard treatment for epilepsy, vision issues, nasolacrimal duct obstruction, hearing loss, cleft palate, anomalies of dentition, cardiac defects, cryptorchidism/hypospadias, bicornuate uterus, vesicoureteral reflux, anemia and/or thrombocytopenia, and immunodeficiency. If surgery is being considered, preoperative evaluation for thrombocytopenia and cardiac

disease with careful monitoring of the upper airway during anesthesia are recommended[3].

CASE

A 5yr old girl presented in the pediatric ward abdominal pain and failure to thrive since the age of 3 years. She was the only child of her parents born out of non consanguineous marriage. She was a preterm baby due to preeclampsia with very low birth weight (1.25kg). After birth she was admitted to NICU for about more than 4 weeks. As per development goals, her motor milestones were delayed to some extent. On physical examination she had short stature, arched eyebrows, long eyelashes, low anterior and posterior hairline, short neck, depressed nasal bridge, microcephaly, excessive body hair and poor eye contact, speech delay and decreased social interaction. Her IGF levels were tested and found to be within normal limits. Soon after that she presented in the pediatric ward with cough, cold, fever for one day and an episode of breakthrough generalized tonic clonic convulsion.

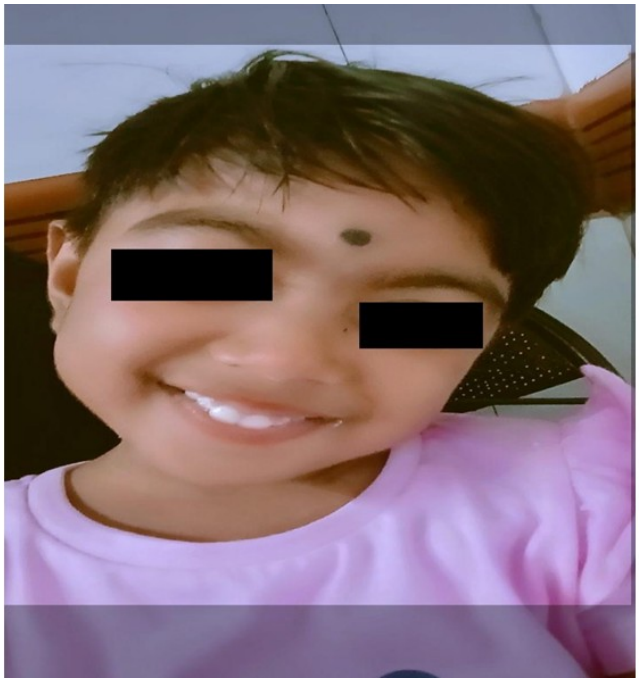

Fig. Photograph of typical facial features of the patient

Management: The child was administered with routine antiepileptic drugs like phenobarbitone, valproate, phenytoin, midazolam, when no improvement was noted, she was administered with clobazam, still no response was found. Levetiracetam was added which control the seizure activity. For abdominal pain a USG of the whole abdomen was done with no significant findings. In addition to cough, cold, fever, the child had symptoms of LRTI which was treated with conservative management.

Investigations and diagnosis

Awake EEG was recorded. The EEG showed alpha waves(8-12 Hz),B/L symmetrical and synchronous, posterior dominant rhythm. Responsive to eye movements. There was B/L frontocentral sharp wave discharge with intermittent theta rhythm at times. Activation procedure unremarkable. Impression was abnormal awake EEG recorded.

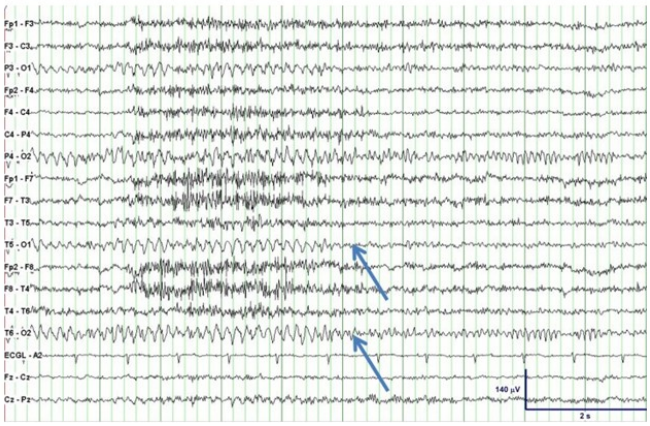

Fig. Interictal EEG recording in sleep with sharp waves with slow component in left parieto-occipital areas

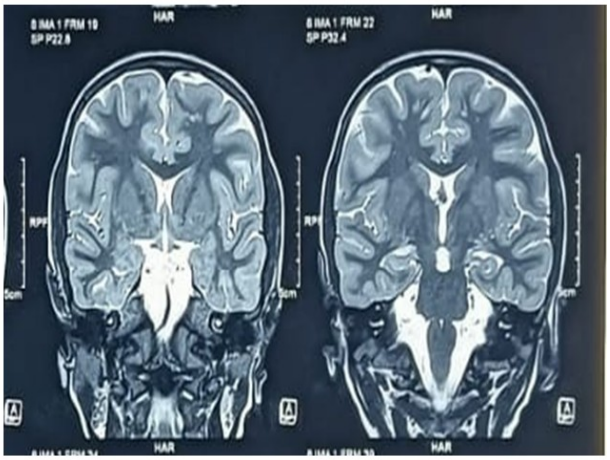

Fig. MRI scan of the brain revealed tiny gliotic foci in bilateral subcortical regions with prominent cortical sulci and perivascular spaces

MRI brain was done for the child. Multiplanar images of the brain were obtained on T1,T2 weighted, FLAIR, DWI and SWI sequences. Multiple small hyperintensities were noted in brain parenchyma on T2Wt and FLAIR images. MRI scan of the brain revealed tiny gliotic foci in bilateral subcortical regions with prominent cortical sulci and perivascular spaces. Features of sinusitis were noted too. The child was advised to do gene testing which revealed a heterozygous frameshift variant c.865_869del in Exon 6 of BRD4 gene that results in the amino acid substitution p.Lys289fs*11, observed variant is novel in gnomAD exomes. The variant is predicted to lead to nonsense-mediated decay of the transcript — pathogenic variant in BRD4 gene associated with Cornelia De Lange Syndrome.

Follow up: the parents were asked to follow up after a year with auxological assessment and biochemical reevaluation of short stature if required. At each visit: measurement of growth parameters, monitoring for signs and symptoms of GERD and for evidence of aspiration with respiratory insufficiency; assessment for new manifestations such as seizures or signs of autonomic dysfunction; monitoring developmental progress and educational needs; behavioral assessment for anxiety, attention, and aggressive or self-injurious behavior; assessment of mobility and self-help skills. At least annually: ophthalmology, dental, audiology evaluation in childhood and adolescence[3].

Differential diagnosis:

- Roberts Syndrome
- Warsaw Breakage Syndrome
- Down Syndrome
- Smith-Lemli-Opitz Syndrome
- Dubowitz Syndrome
- Feingold Syndrome
- Fetal Alcohol Syndrome
- CHARGE Syndrome

Scope:

- Cohesin- Modulating Drugs (Indomethacin): These NSAIDs have been identified in preclinical models to normalize NIPBL expression, a key gene in CdLS pathogenesis
- Cysteine-Based Therapies: Proposed to aid in oxidative stress modulation, a factor in developmental anomalies seen in CdLS.
- Gene Therapy & Epigenetic Modifiers

Enhancing patient outcomes: Cornelia de Lange syndrome is best managed by multidisciplinary approach, including primary care providers, geneticists, neurologists, and multiple other specialists and ancillary staff. Specialty care nurses in neuroscience and development are involved in direct care, patient and family education, monitoring, and facilitating communication between team members. Pharmacists review prescriptions for antiepileptic drugs, check for interactions, and provide education about the importance of compliance and potential side[(1)]. Prognosis: There have been only a very few cases of Cornelia de Lange syndrome reported in adults. Life expectancy is relatively unaffected but if the patients develop any complications of the syndrome then prognosis mainly depends on the severity and management of that complication[(1)]. Cornelia de Lange syndrome (CdLS) affects many different systems of the body, medical management is often provided by a team of doctors and other healthcare professionals.

DISCUSSION

- Cornelia de Lange Syndrome (CdLS) underscores the challenges in diagnosing and managing this rare and complex disorder.
- CdLS presents with a wide range of symptoms, from distinctive facial features and developmental delays to neurological complications like seizures, which can be difficult to control.
- Diagnosis of a BRD4 gene mutation, a rare cause of CdLS, highlights the importance of genetic testing in confirming the condition, especially when clinical features overlap with other developmental disorders.
- The case also emphasizes the need for a comprehensive, interdisciplinary approach to care, involving pediatricians, geneticists, neurologists, and various specialists to address the multiple aspects of the syndrome, such as seizures, developmental delays, and gastrointestinal issues.
- While treatments like antiepileptic drugs and therapies for growth and development can provide some relief, they often offer limited control over the more severe manifestations of the condition.
- Moreover, this case illustrates the importance of regular follow-up for growth monitoring, behavioral assessments, and early intervention strategies.
- As our understanding of the genetic basis of CdLS improves, further research into targeted therapies could lead to better management strategies and potentially more effective treatments, enhancing the quality of life for those affected by this challenging condition.

CONCLUSION

Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder with a wide range of clinical presentations, including developmental delays, distinctive facial features, and various systemic abnormalities. The case discussed highlights the complexities involved in diagnosing and managing a 5-year-old girl with BRD4-related CdLS, emphasizing the importance of a multidisciplinary approach for optimal care. Early identification and appropriate treatment, including the management of seizures and developmental delays, are crucial for improving the quality of life for affected individuals. Ongoing research into the genetic causes and potential therapies for CdLS offers hope for better outcomes and advancements in treatment strategies.

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