Section: Pediatrics

Case Report

COCKAYNE SYNDROME TYPE A DUE TO A HOMOZYGOUS ERCC8 FRAMESHIFT VARIANT IN A TWO-YEAR-OLD CHILD: A CASE REPORT

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ABSTRACT

Background: Cockayne syndrome (CS) is a rare autosomal recessive neurodegenerative disorder caused by defects in transcription-coupled nucleotide excision repair. Pathogenic variants in the ERCC8 gene are responsible for Cockayne syndrome type A. The disorder is characterized by growth failure, developmental delay, progressive neurological deterioration, and multisystem involvement. Early diagnosis is often challenging because of marked clinical heterogeneity and overlap with several neurodevelopmental disorders.

Case Presentation: We report a two-year-old male child born to non-consanguineous parents who presented with fever, progressive generalized weakness, gait instability, recurrent falls, and inability to walk independently. Developmental assessment revealed global developmental delay with an overall developmental quotient of approximately 54% and evidence of neuroregression. Clinical examination demonstrated moderate acute malnutrition and dysmorphic facial features, dental abnormalities, and bilateral otorrhea. On Neurological examination truncal ataxia and reflexes diminished in bilateral lower limbs. magnetic resonance imaging of the brain revealed vermian hypoplasia, however whole exome sequencing was performed and identified a homozygous likely pathogenic ERCC8 frameshift variant, c.952del (p.Val318PhefsTer10), thereby confirming the diagnosis of Cockayne syndrome type A. The child received supportive care, nutritional rehabilitation, physiotherapy, developmental intervention, and treatment for bilateral ear discharge. Although acute infective symptoms improved, neurological deficits persisted.

Conclusion: This case highlights the importance of considering Cockayne syndrome in children presenting with developmental delay, neuroregression, progressive gait abnormalities, and characteristic dysmorphic features. It also underscores the pivotal role of whole exome sequencing in establishing a definitive diagnosis in children with clinically unresolved neurodevelopmental disorders.

Keywords: Cockayne syndrome; ERCC8; neuroregression; developmental delay; whole exome sequencing; global developmental delay; gait instability.

INTRODUCTION

Cockayne syndrome (CS) is a rare autosomal recessive disorder caused by defects in the transcription-coupled nucleotide excision repair pathway. Pathogenic variants in ERCC8 and ERCC6 account for most cases and result in progressive neurological dysfunction, postnatal growth failure, developmental delay, photosensitivity, and features of premature

ageing.[1,2] The disease typically becomes apparent during infancy or early childhood, although the clinical presentation and rate of progression vary considerably among affected individuals.[2,3] Owing to its broad phenotypic spectrum and overlap with several neurodevelopmental disorders, establishing the diagnosis on clinical grounds alone can be difficult. Recent advances in genomic testing, particularly whole-exome sequencing, have substantially improved the diagnostic evaluation of children with suspected monogenic disorders and have an important role in confirming the diagnosis and facilitating genetic counselling.[4,5] We report a child with genetically confirmed Cockayne syndrome type A caused by a homozygous ERCC8 frameshift variant, with the unusual neuroimaging finding of cerebellar vermian hypoplasia.

CASE PRESENTATION

A 2 year 5 month old male child, the third born child of non-consanguineous parents, was admitted with complaints of fever, cough and cold, generalized weakness, and difficulty in walking for seven days.

The child had experienced undocumented fever episodes occurring two to three times per day and dry cough for seven days. Parents noticed progressive difficulty in walking, requiring support for getting up since a week.

Detailed history revealed progressive gait imbalance characterized by frequent falls, inability to maintain balance, and deviation from the walking path. There was no history of seizures, loss of consciousness, altered sensorium, vomiting, abnormal eye movements, drooling of saliva, dysphagia, recent vaccination, spinal deformity, respiratory insufficiency, urinary incontinence, or reduced urine output. There was no significant past medical history. The antenatal, natal, and immediate postnatal periods were uneventful.

Overall developmental assessment was suggestive of global developmental delay with developmental quotient 54%. There were no parental concerns regarding vision or hearing

Family history was non-contributory.

On examination: The child was active and afebrile, and vital parameters were within normal limits. Anthropometric measurements revealed weight of 9 kg (-3 to -2 SD), length of 84 cm (-2 to -1 SD), mid-upper arm circumference of 13.5 cm (-3 to -2 SD), and head circumference of 45 cm (-2 SD), suggestive of moderate acute malnutrition.

General physical examination demonstrated several dysmorphic features, including broad forehead, broad nasal bridge, broad philtrum, high-arched palate, low-set ears, and dental caries. Bilateral ear discharge was also noted. There was no cyanosis, clubbing, edema, lymphadenopathy, or neurocutaneous markers.

Neurological examination revealed a conscious and interactive child with a swaying gait and impaired balance. Muscle tone was normal in all four limbs, and muscle power was greater than 3/5 in all extremities. Deep tendon reflexes were diminished (1+) bilaterally. There were no cranial nerve deficits, cerebellar signs, meningeal signs, or focal neurological deficits.

Ophthalmological evaluation and brainstem evoked response audiometry (BERA) were normal. Magnetic resonance imaging of the brain revealed vermian hypoplasia without other significant intracranial abnormalities. However, despite these findings, a definitive diagnosis could not be established.

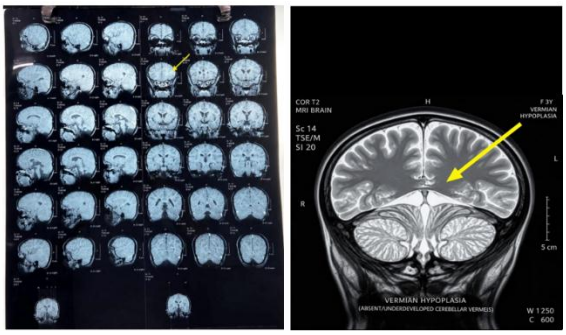

Figure 1: Magnetic resonance imaging of the brain showing vermian hypoplasia

During hospitalization, the child received supportive and symptomatic management. Oral amoxicillin-clavulanate was administered for seven days for ear discharge. Nutritional rehabilitation, occupational therapy, and physiotherapy were initiated. The acute infective symptoms improved; however, developmental impairment and gait abnormalities persisted. The family was counselled regarding the diagnosis, prognosis, autosomal recessive inheritance pattern, and the need for genetic counselling and long-term multidisciplinary follow-up.

DISCUSSION

Cockayne syndrome (CS) is a rare autosomal recessive multisystem disorder characterized by progressive neurodegeneration, postnatal growth failure, developmental delay, photosensitivity, and features of premature aging.[1] Owing to its rarity and marked phenotypic heterogeneity, diagnosis is often delayed, particularly in children presenting with nonspecific neurological manifestations.[2] The disorder results from defects in the transcription-coupled nucleotide excision repair pathway, leading to impaired DNA repair and progressive cellular dysfunction. Accumulation of unrepaired DNA damage predominantly affects tissues with high metabolic demands, especially the nervous system, resulting in progressive neurological deterioration.

ERCC8 mutations account for approximately 20–30% of Cockayne syndrome cases and are typically associated with the classic phenotype and relatively slower disease progression, although clinical

variability exists.[3] In contrast, ERCC6 mutations (70–80%) show a broader clinical spectrum, while rare ERCC2, ERCC3, and ERCC5 mutations cause xeroderma pigmentosum Cockayne syndrome overlap, which generally has a poorer prognosis.

In the present case MRI finding of cerebellar vermian hypoplasia in our patient is unusual, as most reported cases of Cockayne syndrome demonstrate cerebral and cerebellar atrophy, hypomyelination, ventriculomegaly, and intracranial calcifications . Vermian hypoplasia has been reported only in a few isolated cases, making it a rare neuroimaging manifestation that expands the phenotypic spectrum of Cockayne syndrome. Therefore, in children presenting with developmental delay and progressive neurological symptoms, neuroimaging findings should be interpreted in conjunction with clinical and molecular investigations.

Diagnosis based solely on clinical findings may be difficult because several neurodevelopmental and neurodegenerative disorders share overlapping clinical features.[4] Recent advances in pediatric genomics have significantly improved the diagnostic evaluation of children with unexplained developmental delay and neuroregression.[5] In the present case, whole exome sequencing was instrumental in establishing the diagnosis.

Currently, no curative treatment exists for Cockayne syndrome, and management remains largely supportive. Early molecular diagnosis is essential for initiating multidisciplinary interventions. The present case emphasizes the importance of considering Cockayne syndrome in children presenting with developmental delay, neuroregression, and progressive gait abnormalities and highlights the pivotal role of whole exome sequencing in establishing a definitive diagnosis in clinically unresolved cases.[6,7]

To the best of our knowledge, the ERCC8 variant c.952del (p.Val318PhefsTer10) has not been previously reported in the published literature at the time of manuscript preparation. Therefore, we consider this to be a novel or extremely rare variant associated with Cockayne syndrome

CONCLUSION

Cockayne syndrome should be suspected in children with developmental delay, neuroregression, and growth failure. Early whole-exome sequencing enables a definitive diagnosis. Our case highlights the rare association of cerebellar vermian hypoplasia with an ERCC8 mutation and emphasizes the importance of early diagnosis and genetic counselling

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