International Journal of Contemporary Pediatrics
*Nadri G et al. Int J Contemp Pediatr. 2025 Oct;12(10):1728-1732*
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20252976

**Case Report**

# Cockayne syndrome: infantile onset in two siblings and its clinical spectrum in India

**Gulnaz Nadri[1]*, Astha Agrawal[1], Sanjeeda Noor[2], Uzma Firdaus[1]**

[1]Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India
[2]District Early Intervention Centre-Centre of Excellence (DEIC-COE), Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

**Received:** 03 August 2025
**Revised:** 03 September 2025
**Accepted:** 10 September 2025

***Correspondence:**
Dr. Gulnaz Nadri,
E-mail: gulnaznadri7@gmail.com



## ABSTRACT

Cockayne syndrome (CS) is a rare autosomal recessive disorder having myriad manifestations including features of growth failure, premature ageing, photosensitivity and progressive neurological degeneration. Often, a characteristic facial phenotype is also described. Mutations in the ERCC6 or ERCC8 genes, which impair DNA repair mechanisms, are responsible for CS. Mutations in the ERCC6 gene are reported commonly. Due to its rarity and overlap with other neurodegenerative disorders, Cockayne syndrome often presents significant diagnostic challenges, especially in early life. This case report discusses a unique case of 2 two siblings with CS, challenging the typical understanding due to the absence of photosensitivity. The index child presented with growth failure, developmental delay, including motor and speech impairment, with microcephaly and progeroid appearance. Genetic testing confirmed a mutation in the ERCC8 gene, consistent with Cockayne syndrome type A. This case is unique due to the absence of photosensitivity, which is conventionally considered a hallmark feature, highlighting the variability in the phenotypic expression of Cockayne syndrome. Despite established features, Cockayne syndrome remains underdiagnosed, hence under-reported, particularly in milder or atypical cases. The rarity and marked variability in clinical presentation often leads to delayed diagnosis, impacting timely management and genetic counselling. Given its complex presentation, clinicians must maintain a high level of suspicion in children with multisystem involvement who exhibit phenotypic features of Cockayne. This report reinforces the necessity of early recognition and intervention. Timely diagnosis is essential for appropriate management and genetic counselling, potentially altering the trajectory for affected families.

**Keywords:** Cockayne syndrome, Dysmorphism, Developmental delay, ERCC6, ERCC8, Photosensitivity, Progeroid

## INTRODUCTION

CS, a rare autosomal recessive disorder first described by Alfred Cockayne in 1936, is characterized by growth failure, premature ageing (progeria), photosensitivity, progressive neurological degeneration and multisystem involvement, which may include sensorineural hearing loss and pigmentary retinopathy.[1] It is primarily associated with mutations in the ERCC6 (also known as CSB) or ERCC8 (CSA) genes, which play critical roles in DNA repair mechanisms. ERCC6 mutations are more commonly reported.[2]

More than 90 different mutations in the ERCC6 gene have been reported, common being nonsense or frame shift mutations.[3] Thirty-nine mutations are reported in the ERCC8 gene, which include nonsense mutations, missense mutations and large partial gene deletions.[4] With better molecular diagnostic modalities, novel mutations are also frequently being reported.[5] Although

the global incidence of CS is estimated at around 1 in 250,000 births, data on its exact incidence in Indian children is limited.[6] CS presents significant diagnostic challenges, especially in early infancy, due to its overlapping symptoms with other neurodegenerative or genetic disorders. However, the phenotypic features become more evident with increasing age. The clinical spectrum of CS is broad, ranging from early-onset classical form (Type I) to more severe neonatal presentation (Type II) and milder late-onset variants (Type III).

***Type I (Classic Cockayne syndrome)***

Also known as Cockayne syndrome A or CSA, symptoms appear in early childhood, usually within the first or second year of life and progress gradually. Children with classic CS often survive into their teens or early adulthood. The ERCC8 gene is defective in this type.

***Type II (Severe/infantile Cockayne syndrome)***

Also known as Cockayne syndrome B or CSB, this subtype presents at birth or shortly after, with rapid progression and severe symptoms. Children with this form typically do not survive beyond the first decade. The ERCC6 gene is defective in this type.[4]

***Type III (Mild/adult-onset Cockayne syndrome)***

Symptoms emerge later in childhood or adolescence and progress more slowly. This type is rare and has a milder presentation, allowing a longer life expectancy.

Classical cases typically present in early childhood with failure to thrive, progressive microcephaly, developmental delays and characteristic facial features, including a sunken appearance, large ears and a small jaw. Post-natal growth failure is a primary sign of CS. Children with CS often have a short stature, microcephaly and a cachectic appearance. Developmental delays are noticeable early, with many children failing to achieve typical motor or cognitive milestones. Photo sensitivity, one of the most distinct features of CS, can manifest as severe rash and burns when exposed to sunlight often resulting in a characteristic “butterfly” rash across the face. CS is associated with progeroid features, including a “bird-like” facial appearance marked by a small chin, prominent nose, deep-set eyes and a thin face. Loss of subcutaneous fat contributes to this aged appearance, even in young children.

Progressive neurodegeneration is typical in CS, leading to intellectual disability, movement disorders and speech and language delays. Symptoms such as ataxia, spasticity and tremors become more pronounced over time. Many patients ultimately lose the ability to walk and become wheelchair-dependent. Visual and auditory deficits are also common in children who may experience progressive hearing loss and may develop cataracts, optic atrophy and retinopathy, which can eventually lead to blindness. Skeletal deformities, joint contractures and osteoporosis may also develop. Dental issues, including enamel defects and caries, are also frequently observed. Neuroimaging often reveals basal ganglia calcifications and generalized brain atrophy, indicative of CS and may help sometime differentiating it from other neurodegenerative disorders.

***Diagnostic challenges***

Despite these established features, CS remains under-diagnosed, particularly in milder or atypical cases. The diagnosis of CS is often delayed or missed due to the nonspecific early symptoms, such as failure to thrive and developmental delay, which can mimic other common conditions, including cerebral palsy, mitochondrial disorders or primary growth hormone deficiency. The rarity of CS further contributes to diagnostic difficulty, as many physicians may not encounter it during their clinical practices.

***Management and prognosis***

Management of CS largely remains supportive, as there is no curative treatment available. The primary goals of care are to manage symptoms, optimize quality of life and address complications as they arise. The patient requires a multidisciplinary rehabilitative care program, including physical therapy, speech therapy and occupational therapy, which are essential for maintaining mobility and function for as long as possible.[7]

The prognosis for patients with CS depends on the severity and type of the disorder. Type A generally has a life expectancy into the second or third decade of life, with progressive neurological and physical decline. Early recognition and supportive care can improve quality of life, but do not significantly extend life expectancy due to the inherent progression of the disorder. Genetic counselling is also critical for the family, given the autosomal recessive inheritance pattern and the risk of recurrence in future pregnancies.

## CASE REPORT

A 9-month-old male born of a non-consanguineous marriage, first birth by order, presented to the pediatric OPD with complaints of developmental delay, more marked in the motor and speech-language domains. The antenatal and birth history were unremarkable. His birth weight was 2.6 kg, length and head circumference at birth were not known.

At six months of age, he was noticed by his parents to have poor weight gain and not achieving age-appropriate milestones. Mild dysmorphic facial features were appreciable along with growth failure, CS was considered as one of the possibilities and some initial essential

investigations as a part of workup for developmental delay were advised; however, there were no follow-up visits.

As the developmental delay worsened, the parents revisited at 20 months. His weight this time was 8.7 kgs (at 1st percentile), length was 76.5 cm (less than 1st percentile), head circumference was 41.5 cm (less than 3rd percentile). On examination, facial features were more distinct this time, suggesting at a stronger possibility of CS, however, there was no history of photosensitivity or any dermatological problems.

The child had restriction of limb movements, with inability to stand and limited expressive language abilities. Molecular diagnosis was advised for CS; however, it was done a year later because of financial constraints. On follow-up at 3 years of age, the growth failure worsened. The child had a sunken appearance of the eyes with large ears, a thin nose, micrognathia with progeroid appearance and thin dry hair (Figure 1).

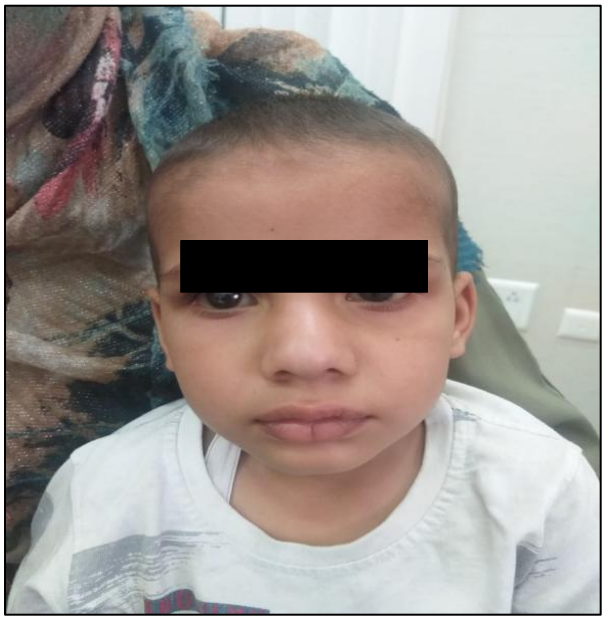

**Figure 1: The 'progeroid appearance'.**

The contracture at the bilateral knee joint had worsened. There was no abnormality detected in vision or audiological examination. On the Bayley Scale of Infant and Toddler Development (BSID), the child had gross developmental delay in all domains. A brain NCCT done elsewhere demonstrated atrophic changes. MRI Brain showed hyperintensities involving deep periventricular white matter of bilateral frontal parietal lobes with mild dilatation of bilateral lateral, 3rd and 4th ventricles along with focal thinning of posterior body and splenium of corpus callosum.

On genetic testing (WES), a homozygous pathogenic variant was detected in the ERCC8 gene at Intron 3 (5'splice site) c.275+1G>T, confirming the diagnosis of CS type A. The child had developed symptoms of growth failure and developmental delay as early as 6 months of age. However, facial features were more pronounced later on. The child also had a 4.5-month-old male sibling. On evaluating the younger sibling, the anthropometric measurements were between the 3rd and 50th percentile; he had not attained neck holding; however, social skills were appropriate for age. There were no prominent dysmorphic features present. On genetic testing, the younger sibling was also found to be homozygous for the same variant in the ERCC8 gene, which was confirmed by Sanger Sequencing.

Given the absence of a definitive treatment for CS, management was primarily supportive. The patient is enrolled in a multidisciplinary care programme, which includes physical therapy, occupational therapy and speech therapy, with regular ophthalmic and audiological evaluations. In addition to genetic counselling, the family received psychological support to help them cope with the emotional challenges posed by the patient's prognosis and the younger sibling's diagnosis. The younger sibling is under regular and close follow-up.

***Indian literature***

While CS is rare globally, its incidence in India is difficult to establish due to limited national data and a lack of a centralized registry for rare genetic diseases. However, several case reports from different regions in India document individual and familial cases of CS, particularly among children. Most cases were diagnosed through clinical and neuro-imaging evaluation due to the high cost and limited availability of genetic testing. Out of 22 children, 12 had molecular confirmation commonly in the ERCC6 gene (Table 1).[8-13]

Most of the cases had features of growth failure, developmental delay, microcephaly, photo-sensitivity and dermatological manifestations. The most common neuro-imaging finding was cerebral atrophy. Visual abnormalities included cataracts, pigmentary retinopathy, corneal opacity and salt and pepper fundus. In dental abnormalities, caries was the most common finding.

**Table 1: Clinical and genetic profile of CS cases reported in India.**

| S. no. | Study | Year | Age Yrs/months | Gene | Variant | P | S | DD | GF | MRI/CT | E | S/H | D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Harkut et al[8] | 2003 | 3.5 | Not done | ----- | + | + | + | + | Not done | + | - | + |
| **2** | Batra et al[9] | 2008 | | | | | | | | | | | |
| | | Sib 1 | 7 | Not done | ------ | + | + | + | + | Ab | + | + | + |

Continued.

| S. no. | Study | Year | Age Yrs/months | Gene | Variant | P | S | DD | GF | MRI/CT | E | S/H | D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sib 2 | 0.6 | | | + | + | + | + | Not done | - | + | |
| **3** | Gaddam et al[10] | 2014 | 14 | Not done | ------- | + | + | + | + | - | - | - | + |
| **4** | Palanisamy et al[11] | 2018 | 7 | Not done | ------- | + | + | + | + | Ab | + | + | |
| **5** | Kondadi et al[12] | 2020 Cousins 1-4 | 12 | Not done | ------- | + | + | + | + | Ab | + | + | + |
| **6** | Narayanan et al[13] | 2021 | | | | | | | | | | | |
| | | F1-sib 1 | 1.1 | ERCC6 | c.3112 delA | - | + | + | + | Ab | - | - | - |
| | | Sib 2-exp | | | | | | | | | | | |
| | | F2-sib1 | 0.6 | ERCC6 | c.2885T >G | + | + | + | + | N | | | |
| | | Sib2-exp | | | | | | | | | | | |
| | | F3 (Sib1) | 11 | ERCC6 | c.543+2 T>G | + | + | + | + | - | - | - | + |
| | | F3 (Sib2) | 6 | ERCC6 | c.543+2 T>G | + | + | + | + | - | - | - | + |
| | | F4 | 9 | ERCC6 | c.4063-1G>C | + | + | + | + | Ab | + | - | - |
| | | F5 | 5 | ERCC8 | c.37G>T (p.E13*) | + | + | + | + | - | + | + | - |
| | | F6 (Sib1) | 6 | ERCC6 | c.3071-1G>A | + | + | + | + | Ab | - | - | - |
| | | F6 (Sib2) | 3 | ERCC6 | c.3071-1G>A | + | + | + | + | Ab | + | - | - |
| **7** | Case | 2024 | | | | | | | | | | | |
| | | Index | 0.9 | ERCC8 | c.275+1 G>T | - | - | + | + | Ab | - | - | - |
| | | Sib | 0.5 | ERCC8 | c.275+1 G>T | - | - | + | - | Not done | - | - | - |

F-Family, P-Photosensitivity, S-skin manifestations, DD-Developmental delay, GF- Growth Failure, E-Eye involvement, S/H- speech and hearing, D-Dental, R-Radiological, C1-4-Cousins of the index case, Ab-Abnormal, N-Normal.

## DISCUSSION

CS is a rare autosomal recessive disorder with a broad spectrum of clinical presentations, primarily affecting growth, development and neurological functions. This case highlights several of the characteristic features of Cockayne syndrome and underscores the diagnostic challenges associated with this condition, given its rarity and the overlap with other disorders. The index child in this report exhibited many of the hallmark features of Cockayne syndrome, including severe growth failure, microcephaly and developmental delays.[1] These features are consistent with Type A CS, which generally presents in early childhood.

Interestingly, there was no history of photosensitivity, which is typically considered a hallmark feature of CS, thus challenging the conventional understanding of its manifestations and suggesting a broader phenotypic variation than previously understood. Narayanan DL et al, also mentions absence of photosensitivity in one of the family mentioned in their study.[13] Another important feature seen in this family was the absence of cutaneous hypersensitivity to sunlight which may indicate that the progression to full manifestation of CS may evolve with time.[14]

The child's distinct facial features, such as the sunken eyes, thin nose and micrognathia, align with the phenotypic description of CS in the literature.[2] The siblings in our report exhibited features consistent with classical form, emphasizing the heterogeneous natural history of the disease. The confirmation is made through molecular testing, which reveals pathogenic variants. Mutations in the ERCC6 and ERCC8 genes are responsible for defective transcription-coupled nucleotide excision repair (TC-NER), leading to the accumulation of DNA damage, particularly in cells exposed to UV light.[6,14,15] The genetic confirmation in our case not only confirmed the diagnosis but also allowed for appropriate genetic counselling for the family. The younger sibling only had complaints of motor development delay at 4.5 months, emphasizing that the features may evolve and become more evident, including the facial appearance.

## CONCLUSION

CS is a rare autosomal recessive disorder that presents significant diagnostic challenges. Early recognition of key clinical features, such as growth failure, developmental delay, photosensitivity and progressive neurological decline, is critical for timely diagnosis and intervention. This case highlights the importance of early genetic testing, especially in atypical presentations, to ensure timely intervention and genetic counselling of the affected families. Since there is no cure, multidisciplinary management can improve quality of life and help mitigate some of the disease's effects through supportive care. Molecular confirmation also enables prenatal or preimplantation genetic diagnosis in future pregnancies.

This case contributes to the increasing literature on CS in familial clusters. It underscores the need for increased awareness among clinicians, as early diagnosis can lead to better management outcomes and provide families with a clearer understanding of the condition and its progression. It also reinforces the critical role of molecular diagnosis in confirming Cockayne syndrome, especially when presenting with atypical or uncommon features.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

## REFERENCES

1. Boraz RA. Cockayne's syndrome: literature review and case report. Pediatr Dent. 1991;13(4):227-30.
2. Wilson BT, Stark Z, Sutton RE, Danda S, Ekbote AV, Elsayed SM, et al. The Cockayne Syndrome Natural History (CoSyNH) study: clinical findings in 102 individuals and recommendations for care. Genet Med. 2016;18(5):483-93.
3. Laugel V, Dalloz C, Durand M, Sauvanaud F, Kristensen U, Vincent MC, et al. Mutation update for the CSB/ERCC6 and CSA/ERCC8 genes involved in Cockayne syndrome. Hum Mutat. 2010;31(2):113-26.
4. Cao H, Williams C, Carter M, Hegele RA. CKN1 (MIM 216400): mutations in Cockayne syndrome type A and a new common polymorphism. J Hum Genet. 2004;49(1):61-3.
5. Taghdiri M, Dastsooz H, Fardaei M, Mohammadi S, Farazi Fard MA, Faghihi MA. A Novel Mutation in ERCC8 Gene Causing Cockayne Syndrome. Front Pediatr. 2017;5:169.
6. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA. Cockayne syndrome: Clinical features, model systems and pathways. Ageing Res Rev. 2017;33:3-17.
7. Hoar DI, Waghorne C. DNA repair in Cockayne syndrome. Am J Hum Genet. 1978;30(6):590-601.
8. Harkut P, Salodkar A. Cockayne's syndrome. Indian Pediatr. 2003;40(10):1010.
9. Batra P, Saha A, Kumar A. Infantile onset of Cockayne syndrome in two siblings. Indian J Dermatol Venereol Leprol. 2008;74:65-7.
10. Gaddam D, Thakur MS, Krothapalli N, Kaniti S. Dental Management of a 14-Year-Old with Cockayne Syndrome under General Anesthesia. Case Rep Dent. 2014;2:925258.
11. Palanisamy P, Pullabhota A, Manjaeyadu HK, Mutnuru PK. Cockayne syndrome-A case report. Indian J Case Reports. 201;4(2):112-4.
12. Kondadi P, Karjigi S, Herakal KC. A case report of Cockayne syndrome- five cases in a single family. Int J Res Dermatol. 2020;6(6):798–800.
13. Narayanan DL, Tuteja M, McIntyre AD, Hegele RA, Calmels N, Obringer C, et al. Clinical and Mutation Spectra of Cockayne Syndrome in India. Neurol India. 2021;69(2):362-6.
14. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA. Cockayne syndrome: Clinical features, model systems and pathways. Ageing Res Rev. 2017;33:3-17.
15. Laugel V, Dalloz C, Durand M, Sauvanaud F, Kristensen U, Vincent MC, et al. Mutation update for the CSB/ERCC6 and CSA/ERCC8 genes involved in Cockayne syndrome. Hum Mutat. 2010;31(2):113-26.

**Cite this article as:** Nadri G, Agrawal A, Noor S, Firdaus U. Cockayne syndrome: infantile onset in two siblings and its clinical spectrum in India. Int J Contemp Pediatr 2025;12:1728-32.