

Cockayne Syndrome: A Rare neurodegenerative Disorder- A Case Report

GK KUNDU^a, FN DOLA^b, Q MIAH^c, A SARKER^d

Abstract:

Cockayne Syndrome (CS) is a rare autosomal recessive disorder characterised by multi-systemic involvement, including developmental delay, microcephaly, cachectic dwarfism, hearing and visual impairment, cardiac, renal and endocrine complications due to a defect in the DNA repair mechanism. The striking feature of CS is bilateral

basal ganglia calcifications. We are presenting a 9-month-old boy presenting with developmental delay, microcephaly, multiple renal abnormalities and the brain CT scan showing bilateral basal ganglia calcifications.

Keywords: Cockayne syndrome, neurodegenerative disorder.

(J Bangladesh Coll Phys Surg 2025; 43: 303-305)

DOI: <https://doi.org/10.3329/jbcps.v43i4.85000>

Introduction:

Cockayne syndrome (CS) is one of the DNA repair disorders, inherited as autosomal recessive manner. It is manifested with heterogeneous features including neurodevelopmental/intellectual disabilities, microcephaly, growth failure, visual and hearing abnormality, hypomyelination, hepatic, renal, cardiac involvement, skin photosensitivity and dental caries¹. The patients with Cockayne syndrome have a failure to repair oxidation-induced injury to DNA bases, specially those that are transcribed into RNA². The patients gradually develop premature ageing manifested as progeroid face³. The usual diagnosis of Cockayne syndrome includes characteristic features with neuroimaging findings and exclusions of other possible causes. Here, we are describing a case of an infant presenting with multisystem involvement and basal ganglia calcifications.

Case description

A 9-month-old boy of nonconsanguineous marriage came into a tertiary care hospital having developmental delay, dribbling and excessive crying during micturition (Figure 1). After an uneventful birth history, he came into medical attention with recurrent urinary tract infection. Further evaluation revealed no neck control, social smile, impaired vision and hearing. He had no history of excessive vomiting, seizure, impaired consciousness, abnormal behaviour, skin pigmentation, photosensitivity or any positive family history. He had microcephaly (occipito-frontal circumference) OFC - 41cm (z score -3.2 SD); weight for length Z score is -1.6. His vital signs, including blood pressure (BP), were normal. Motor examination revealed increased tone, power 4/5, deep reflexes normal in both upper and lower limbs, and the Babinski sign was positive. His genitourinary system examination revealed the presence of phimosis and a double urethral opening. His Brain CT scan showed bilateral basal ganglia calcification and cortical atrophy. (Figure 2) His renal evaluation showed features of recurrent cystitis, and he had Grade II vesicoureteric reflux (VUR) (Figure 3). Serum creatinine, electrolytes, calcium, and parathyroid hormone were normal. Basic metabolic screen (serum ammonia, lactate, urinary ketone body), and electroencephalogram (EEG) were also normal. Ophthalmic evaluation showed cortical visual impairment. He was managed with the Pediatric Nephrology and Pediatric Urology department with proper counselling, correction of phimosis with circumcision, developmental therapy for delayed development, prophylaxis for recurrent UTI, and other supportive treatments, with some improvement.

- a. Professor Gopen Kumar Kundu, Professor, Department of Paediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh.
- b. Dr. Farah Naz Dola, Resident, MD Phase-B (Paediatric Neurology & Neurodevelopment), Dept. of Paediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh.
- c. Dr. Quddus Miah, Resident, MD Phase-B (Paediatric Neurology & Neurodevelopment), Dept. of Paediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh.
- d. Dr. Anita Sarker, Resident, MD Phase-B, (Paediatric Neurology & Neurodevelopment), Dept. of Paediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh.

Address of Correspondence: Dr. Farah Naz Dola, MD Phase B Resident, Department of Pediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh. dolafarahnazdola@gmail.com. Cell: +8801747561930

Received: 26 September, 2024

Accept: 02 August, 2025



Figure 1 : A 9 month old male child with microcephaly & developmental delay.

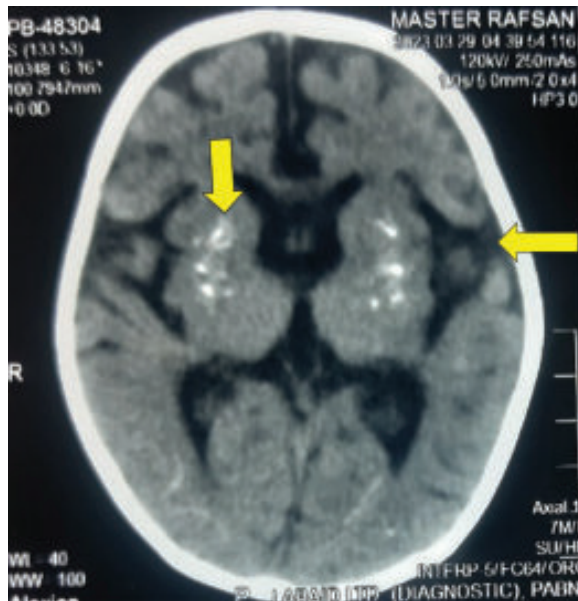


Figure 2 : CT scan of brain showing bilateral basal ganglia calcifications (arrow- vertical), cortical atrophy (arrow-horizontal)

Discussion:

CS was first described by Edward Alfred Cockayne in 1936⁴. It is characterised by progressive neurodegeneration, intellectual disability, developmental delays,



Figure 3: MCU showing grade II VUR on right side (arrow).

retinal degeneration, microphthalmia, cataract, sensorineural hearing loss, vital organ abnormalities, severe photosensitivity and premature ageing³. CS has complex and heterogeneous neuropathology that shows calcification of the basal ganglia, cerebral and cerebellar atrophy, microcephaly, and patchy demyelination.

CS is inherited as an autosomal recessive disorder, and its prevalence is 2–3/million globally, including the US, though the incidence is higher in some European countries⁵.

CS is classified into three major phenotypes based on the severity and age of presentation. Type I is also known as the classic type. Usually present in the first two years of life, and is moderate in severity. Life expectancy is up to 16 years. Type II, also known as the congenital form, is the most severe and has the earliest onset and may die within five years. Type III has a late onset and milder features, with the highest life expectancy up to adult life³. Another phenotype of CS is associated with Xeroderma pigmentosum (XP); another disease due to the breakage of the DNA repair mechanism⁶.

Our index case corresponds with type II, as he has features including developmental delay, microcephaly, visual and hearing impairment, renal abnormalities and basal ganglia calcifications since birth; though he has not developed cachectic dwarfism or progeroid facies yet.

CS occurs due to mutations in any one of five genes that encode the proteins responsible for the repair of injured DNA². CS patients have mutations in genes encoding Cockayne syndrome B (CSB), excision repair cross-complementing protein group 6 (ERCC6) on chromosome 10q11, and Cockayne syndrome A (CSA), ERCC8 gene on chromosome 5q11. Mutations in the ERCC3, ERCC4 and ERCC5 exhibit some overlapping features with Xeroderma pigmentosum. Approximately 70% individuals have a mutation in CSB, and its severity is more severe, and most of the remaining have CSA mutations⁵.

Thousands of DNA have been injured by reactive oxygen species through normal metabolic processes. These are corrected by the DNA repair mechanism. In Cockayne Syndrome, cells show a marked impairment in the regain of RNA synthesis after exposure to UV irradiation or normal metabolism, which leads to the failure in the repair of transcription genes⁴.

Due to financial constraints, we could not do a genetic study in our presented case. But the exclusion of the other differential diagnoses strongly establishes our diagnosis as CS.

Though CS is a disease of impaired DNA repair mechanism and hypercreativity to UV-rays, like other diseases of this entity, CS patients have never been reported to have malignancy. This is due to the absence of increased mutation on exposure to sunlight. Our indexed case has not yet shown photosensitivity.

Patients with CS may have multiple renal abnormalities. In one study, 62% had renal abnormalities, including chronic kidney disease, nephrotic syndrome, hypoplastic kidneys, hypertension, and nephrolithiasis⁷. Our case had obstructive uropathy (phimosis, leading to Grade II VUR and a double urethral opening).

Though in CS, cardiac, endocrine, and gastrointestinal involvements are common, our patient had normal findings in both clinical and investigations findings in those regards.

Till now, management is symptomatic and supportive, and management of the associated comorbidities. Antioxidants and pharmacological chaperones can be used. At present, some drugs are under clinical trials (Prodarsan and Sirolimus)⁵.

Our patient has been managed with proper counselling, correction of phimosis with circumcision, developmental therapy, prophylaxis for recurrent UTI, and antioxidant supplementation.

The prognosis of CS usually depends on the phenotypic presentation. The cause of death is usually pneumonia/respiratory illnesses⁴. Our patient is still doing well despite a developmental delay and congenital renal malformation.

Conclusion:

The purpose of this case report is to raise the possibility of having a diagnosis of a rare hereditary disease, namely, Cockayne Syndrome. It will be supported when the patient presents with early heterogeneous presentation, including neurodevelopmental delay, small head and neuroimaging discloses basal ganglia calcification, myelination defect with brain atrophy. Impaired vision, hearing and other vital systems may give important clue to diagnosis and counselling.

Conflict of interest:

Nothing to declare

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