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# Evaluation of Patients with Cockayne Syndrome

Author(s)

Hamit Acer[1], Gül Demet Özçora[2], Mehmet Canpolat[3], Muhammet Ensar Doğan[4], Zehra Filiz Karaman[5], Sefer Kumandaş[3]

Affiliation(s)

[1]Denizli State Hospital, Clinic of Pediatrics, Division of Pediatric Neurology, Denizli, Türkiye
[2]Memorial Ataşehir Hospital, Clinic of Pediatrics, Division of Pediatric Neurology, İstanbul, Türkiye
[3]Erciyes University Faculty of Medicine, Department of Pediatric Neurology, Kayseri, Türkiye
[4]Kayseri City Training and Research Hospital, Clinic of Medical Genetics, Kayseri, Türkiye
[5]Erciyes University Faculty of Medicine, Department of Radiology, Kayseri, Türkiye

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## Abstract

Cockayne syndrome (CS) is a rare, severe, genetic neurodegenerative disorder. To better understand the condition, this article aimed to discuss the clinical manifestations and prognosis of CS. This clinical study was a retrospective review of the medical records of patients diagnosed with CS between January 2010 and January 2020. A total of 9 patients (6 males, 66.7%; 3 females, 33.3%) from 7 families were enrolled in the study. The median age of the patients was 94 (4-186) months. Genetic confirmation of CS was obtained in 5 of the patients and ERCC8 mutations were identified in all patients who underwent genetic confirmation of the disease. On admission, 8 patients were found to have microcephaly 4 patients were admitted for psychomotor retardation, 3 for seizures, and two for walking disabilities. The diagnosis of patients with CS can be challenging due to the wide range of symptoms. In patients who are normal at birth but develop microcephaly during follow-up, physicians should consider CS in addition to metabolic diseases in the differential diagnosis.

**Keywords:** Cockayne syndrome, microcephaly, premature aging

**Correspondence:** Hamit Acer, Denizli State Hospital, Clinic of Pediatrics, Division of Pediatric Neurology, Denizli, Türkiye
**E-mail:** dr_hamitacer@hotmail.com **ORCID:** 0000-0002-4743-0847

## Introduction

Cockayne syndrome (CS) is a rare, severe, genetic neurodegenerative disorder. The clinical features of this disease include failure to thrive, microcephaly, impaired development of the nervous system, sensitivity to sunlight, visual impairment, sensorineural deafness and premature aging[1]. There are two main types of CS: CS type A (CSA) and CS type B (CSB)[2]. CSA arises from mutations in ERCC8, whereas CSB results from mutations in ERCC6. It is possible to have problems that affect any internal organ and typically manifest in childhood. It is associated with a group of disorders called leukodystrophies, which are characterized by deteriorating white matter in the nervous system[3].

Although the pathogenesis of this condition is not fully understood, it is known that basic deficiency is caused by deficiencies in DNA repair. In contrast to other defects in DNA repair, patients with CS have no predisposition to cancer or infection. The time of disease onset and the rate of disease progression differ significantly between the subgroups. CS is classified into three types: Type I (classical type), type II (congenital or severe type), and type III (late-onset or adult-onset type) based on the clinical features[4]. CS type I, the "classic" form, is characterized by normal fetal growth. Abnormalities typically develop within the first two years of life. Degeneration of the central and peripheral nervous systems leads to death in the first or second decade of life. CS type II is a congenital condition. It is significantly more severe than CS type 1. There is minimal neurological development after birth. Death typically occurs before age seven. Type III CS is characterized by later onset and is typically milder than types I and II[5].

Diagnosis of patients with CS can be challenging due to the wide range of symptoms. It is important to raise awareness among clinicians regarding disease severity. However, only a limited number of studies have been conducted on CS. To better understand the condition, this article aimed to discuss the clinical manifestations and prognosis of CS.

**Highlights**

- Cockayne syndrome (CS) is a rare, severe, genetic neurodegenerative disorder.
- CS is a heterogeneous disease that affects various systems, including the cardiovascular, genitourinary, and gastrointestinal systems.
- Patients with CS have been shown to have peripheral neuropathy, which may lead to muscle weakness and locomotion disturbances.
- Microcephaly, along with growth retardation, is a fundamental feature of CS.
- The presence of bilateral calcifications in the basal ganglia, dentate nucleus, and subcortical white matter is considered a diagnostic hallmark of CS.
- However, patients who are normal at birth develop microcephaly during follow-up, and it is recommended that vision and hearing tests be performed. In the differential diagnosis, physicians should consider CS in addition to metabolic diseases.

## Material and Method

This clinical study was a retrospective review of the medical records of patients diagnosed with CS between January 2010 and January 2020 at the pediatric neurology department of Erciyes University. Individuals with a confirmed diagnosis of CS via molecular genetic testing were included in the study. A small number of patients were included in the study without confirmation of a clear clinical diagnosis of CS.

The perinatal history, presenting symptoms, systemic findings, psychomotor development, radiological assessment, mean age at diagnosis, and genetic results were collected from the electronic hospital records by a pediatric neurologist. Computed tomography (CT) or magnetic resonance imaging (MRI) was performed in all patients.

Informed consent was obtained from all participants before enrollment, and the study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2021/22 date: 06.01.2021).

### Statistical Analysis

The statistical analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS) 22.0 package. In order to determine whether there was a normal or abnormal distribution, the Shapiro-Wilk test was applied to all variables. Non-normal data were expressed as median (minimum-maximum) and categorical data were expressed as counts and percentage.

## Results

A total of 9 patients (6 males, 66.7%; 3 females, 33.3%) from 7 families were enrolled in the study. The median age of the patients was 94 (4-186) months. On admission, 8 patients were found to have microcephaly 4 patients were admitted for psychomotor retardation, 3 for seizures, and two for walking disabilities. All of our cases were defined as type 1 when evaluated according to their clinical features. The clinical features in our cohort are summarized in **Table 1**.

Genetic confirmation of CS was obtained in 5 of the patients and ERCC8 mutations were identified in all patients who underwent genetic confirmation of the disease. An antenatal ultrasound scan was performed on all patients in the cohort, and no abnormalities were found on the scans in any of the patients. Seven (77%) patients had a cesarean section and 2 (23%) had normal vaginal deliveries. It was found that no patients were admitted to the neonatal intensive care unit after birth. The weights of the patients at birth were all within the normal range, and based on the head circumference data at birth, all patients were found to be normocephalic.

Patients in the study were tested for hearing and vision problems. It was detected that 4 patients (45%) had normal audiological evaluations and 5 (55%) had bilateral sensorineural deafness. In the ophthalmological evaluation of patients, microphthalmia was detected in 7 (77%) cases, cataract in 2 (22%) patients, optic atrophy in 2 (22%) patients, and retinitis pigmentosa in

**Table 1.** *Clinical features and genetic consequences of Cockayne syndrome*

| Case | Sex | Age | Birth weight | Developmental delay | Microcephaly | Characteristic physical appearance | Eyes symptoms | Teeth | Deafness | Contractures | Cutaneous photosensitivity | Seizure | CNS anomalies | Mutation | Type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 6 y | 2780 g | + | + | + | Microphthalmia | Hypoplastic teeth | + | - | - | + | Cortical atrophy/basal ganglia calcifications | ERCC8 | CS 1 |
| 2 | M | 4 m | 3120 g | + | - | + | - | | - | - | - | - | Cortical atrophy/basal ganglia calcifications | | CS 1 |
| 3 | M | 15 y | 2670 g | + | + | + | Optic atrophy and microphtalmia | Dental caries, delayed eruption | - | + | - | + | Cortical atrophy/basal ganglia calcification, hypomyelination | ERCC8 | CS 1 |
| 4 | M | 10 y | 3410 g | + | + | + | Cataracts, microphtalmia | Dental caries | + | + | + | - | Cortical atrophy/basal ganglia calcifications, hypomyelination | ERCC8 | CS 1 |
| 5 | M | 10 y 10 m | 3080 g | + | + | + | Optic atrophy and microphtalmia | Dental caries and hypoplastic teeth | + | + | + | - | cortical atrophy/basal ganglia Calcifications, hypomyelination | ERCC8 | CS 1 |
| 6 | F | 7-10 m | 2960 g | + | + | + | Retinitis pigmentosa, microphtalmia | Delayed eruption, dental caries, | + | - | - | - | Cortical atrophy/basal ganglia calcifications, hypomyelination | | CS 1 |
| 7 | M | 6-2 m | 2850 g | + | + | + | Retinitis pigmentosa, microphtalmia | Hypoplastic teeth | - | - | - | - | Cortical atrophy/basal ganglia calcifications, hypomyelination | | CS 1 |
| 8 | F | 3 y 10 m | 3400 g | + | + | + | - | Malocclusion | - | - | + | + | Cortical atrophy/basal ganglia calcifications | | CS 1 |
| 9 | F | 15 y 6 m | 2910 g | + | + | + | Cataracts, microphtalmia | Delayed eruption, dental caries, | + | + | - | + | Cortical atrophy/basal ganglia calcifications, hypomyelination | ERCC8 | CS 1 |

CNS; Central nervous system, M; Male, F; Female, M; Month Y; Year

3 (33%) patients. Echocardiographic and genitourinary ultrasonographic evaluation of the patient did not reveal any abnormal findings. Hepatic involvement was accepted based on elevated transaminase levels and elevated levels of transaminase were found in 5 (55%) patients without concomitant cholestasis.

Seizures occurred in 4 (44%) patients, and the analysis of the patients' electroencephalography showed focal sharp wave activity in addition to irregular ground activity. Seven patients underwent CT imaging, and cranial MRI was performed in all patients. Calcifications were observed in the bilateral basal ganglia in all cases. The MRI evaluation showed cerebral atrophy and cerebellar involvement in all patients, and hypomyelination was found in 6 cases **(Figures 1, 2 and 3).**

In our study, 1 (11%) patient was able to ambulate, while the others were unable to walk. Seven (77 %) patients had muscle weakness, 4 (44%) had joint contractures, 6 patients had tremor, 3 (33.3%) had scoliosis, 5 (55%) had photosensitivity **(Figures 4, 5 and 6).**

## Discussion

CS is a rare disorder that can be extremely difficult to detect early in life due to phenotypic variability. Fundamental conditions like growth retardation and microcephaly develop rapidly over time, resulting in the loss of acquired skills like sitting, walking, swallowing, self-feeding, and speaking. In this study, we evaluated data from 9 subjects for a better understanding of clinical characteristics of the disorder. To the best of our knowledge, this study is one of the few to evaluate the clinical outcomes of CS in the literature.

CS is a rare and fatal disorder that typically causes death within the first or second decade. Out of the 140 cases reviewed by Nance and Berry[6], 37 had a mean age at death of 12 years, and 22% of these patients died at least 20 years old. The underlying disease is a defect in one of the repair mechanisms of the DNA. Patients with CS do not have a predisposition to cancer or infection, in contrast to those with other DNA repair defects[3].

The genetic types of CS are type A ERCC8 (also known as CSA), type B ERCC6 (also known as CSB), and type C. Based on previous research, there was no significant correlation between the type of mutation and the severity of CS[7]. In our cohort, whole exome sequencing was performed in 5 of the patients and the ERCC8 mutation was detected in all. Additionally, a review of all cases revealed that they exhibited type 1 characteristics when evaluated according to their clinical features.

It is believed that the CSA and CSB proteins help RNA polymerases overcome transcriptional blockages caused by DNA damage. Cells that are deficient in CSA and CSB are unable to repair the DNA damage caused

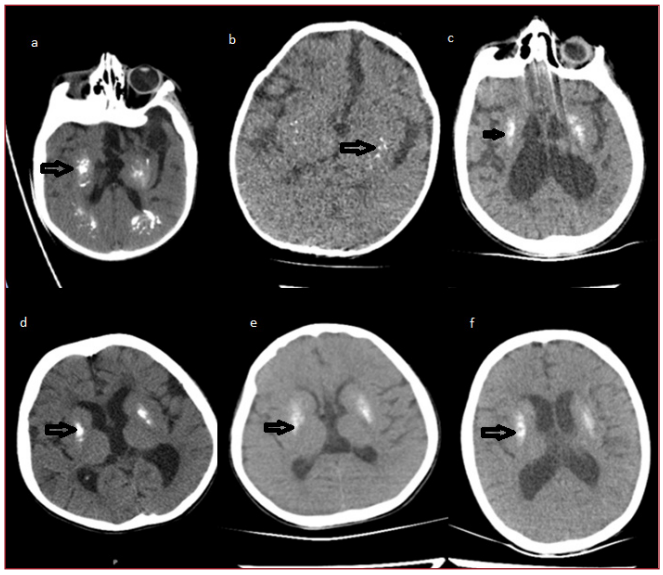


**Figure 1.** Axial non-contrast brain CT images
Basal ganglia and white matter calcifications and varying degrees of cerebral atrophy
*CT: Computed tomography*

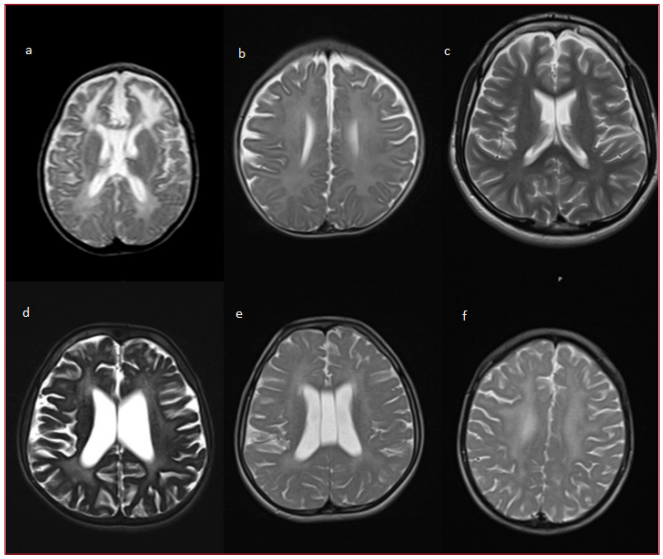


**Figure 2.** Axial T2 non-contrast brain MRI images
T2A hyperintense hypomyelinated areas in periventricular white matter
*MRI: Magnetic resonance imaging*

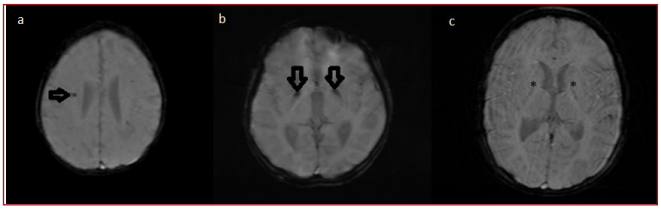


**Figure 3.** SWI sequence images
A) Punctate calcification at the level of the right centrum semiovale (a)
B) Calcification is present in both basal ganglia (b,c)
*SWI: Susceptibility weighted imaging*

**Figure 4.** Microcephally, small chin, prominent ear structure, sunken and prominent eyes, and prematurely aged appearance

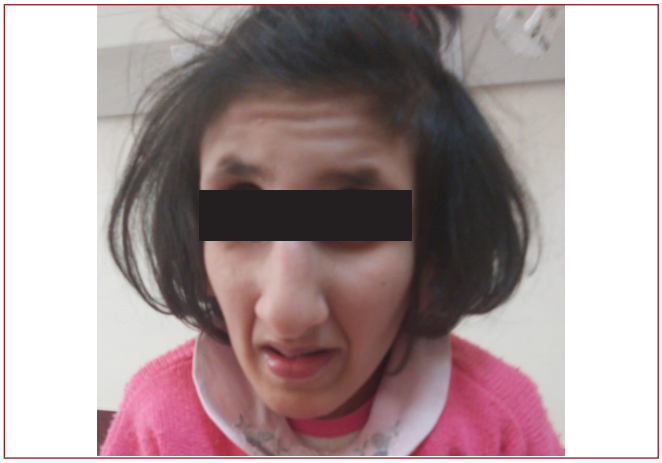

**Figure 5.** Microcephally, small chin, elongated nose, sunken and prominent eyes, prematurely aged

**Figure 6.** Kyphosis: They might be very cachetic because of the loss of subcutaneous

by ultraviolet light, in contrast to normal repairing cells[8]. Deficiencies in DNA repair are likely to be responsible for some patients with CS who have an extreme sensitivity to sunlight and may have premature aging. In a study that was conducted by Wilson et al.[8] it has been reported that 40 out of 99 patients were photosensitive and developed blisters after exposure to sunlight. In our study, 3 (33%) of 9 patients had photosensitivity.

The neurological symptoms of CS are severe and have a significant impact on morbidity. The presence of bilateral calcifications in the basal ganglia, dentate nucleus, and subcortical white matter is considered a diagnostic hallmark of CS[9]. In rare cases, confirmed by genetic testing, CS without calcification has been reported[9]. Even in severe cases, brain calcifications may not be visible before the age of 1 year; however, almost all patients with CS tend to develop calcifications after the age of 3[10]. Severe white matter atrophy has also been demonstrated in CS on imaging[11]. In one series, all patients who underwent MRI showed brain atrophy, with white matter loss being the earliest neuro-radiological finding[10]. In our study, including two patients aged 1 year, in all cases calcifications were seen in the basal ganglia, and hypomyelination was detected in 5 of the patients.

Patients with CS have been shown to have peripheral neuropathy in several studies[12].This condition may lead to muscle weakness and locomotion disturbances[13]. This study showed that individuals with CS experience walking disability, muscle weakness, and contractures. We observed that 1 patient was capable of ambulation, 7 patients had muscle weakness, 4 patients had joint contractures, and 3 patients had scoliosis **(Figures 4, 5 and 6).**

Microcephaly, along with growth retardation, is a fundamental feature of CS. Except for the severe infantile variants, the circumference of the head at birth is usually within the normal range, and its growth gradually slows with age, often stopping completely between the ages of 1 and 2 years[3]. Head circumference at birth is within the normal range, indicating the absence of any developmental disorder in patients with CS. Although it is true that the majority of patients with CS over the age of 2 have microcephaly, it is important to note that a small percentage may have normal measurements. Therefore, if a patient is suspected of having CS but does not have microcephaly, alternative diagnoses may be necessary. One study documented that the autopsied brains of patients with CS were generally 50% or less weightless than expected[5]. Normal in utero growth followed by early postnatal microcephaly without gross brain structural abnormalities suggested that transplacental growth factors may be lost. Although the birth weights and head circumferences of all patients were within the normal range, microcephaly was detected in 8 of the patients in our study.

The involvement of the nervous system in most patients may result in cognitive impairment, developmental delay, motor dysfunction, and ambulatory difficulties. The loss of neurons in auditory and visual pathways can also lead to hearing and vision problems[14]. Cataracts are frequently reported in patients with CS. The presence of cataracts before the age of 3 years is considered a significant prognostic factor for survival in individuals with CS[6]. In our study, 7 patients had ocular involvement, including 2 patients (patient 4, patient 9) who were diagnosed with cataracts. Hearing loss is a significant feature of CS[6]. Audiometry testing may be unavailable for various reasons, including difficulties associated with testing in children and individuals with neurological or cognitive impairments. However, if it is not recognized in the early stages of CS, hearing loss can lead to a more withdrawn demeanor. In our study, 4 patients (45%) had normal audiological evaluations and 5 had bilateral sensorineural deafness. It has been observed that a significant proportion of patients with CS, approximately 23%, may experience seizure disorders, and approximately 66% may experience tremors[8]. The majority of patients experience ongoing seizures without a predominant seizure type, and intention tremor is the most common type of tremor observed. In our cohort, seizures occurred in 4 out of 9 (44%) patients, without a predominant seizure type, and intention tremors were observed in 6 patients, which is consistent with the literature.

CS is a heterogeneous disease that affects various systems, including the cardiovascular, genitourinary, and gastrointestinal systems. The cardiovascular system exhibits an advanced degree of arteriosclerosis according to the age of the patient[13]. Renal failure may occur in some patients and is believed to be secondary to hypertension and atherosclerosis[15]. The endocrine system appears to be functioning normally, and no deficiencies in hormones have been reported. In our study, echocardiographic and genitourinary evaluation of the patients did not reveal any abnormal findings; however, elevated levels of transaminase were found in 5 patients and feeding difficulties were detected in all patients.

### Study Limitations

This study demonstrated the clinical features of CS. However, there are a number of important limitations to this study that should also be noted, including the limited number of patients, single-center design, and lack of genetic confirmation of all patients. Another limitation was that electromyography could not be performed in our patients.

## Conclusion

Many questions remain regarding the molecular mechanisms underlying this disease. However, patients who are normal at birth develop microcephaly during follow-up, and it is recommended that vision and hearing tests be performed. In the differential diagnosis, physicians should consider CS in addition to metabolic diseases.

**Ethical Approval:** The study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2021/22 date: 06.01.2021).

**Informed Consent:** Consent was obtained from the parents of the patients.

**Author Contributions:** Acer H: Design, Data Collection or Processing, Writing.; Özçora GD: Design, Literature Search.; Canpolat M: Concept, Writing.; Doğan ME: Analysis or Interpretation.; Karaman ZF: Analysis or Interpretation.; Kumandaş S: Concept.

**Conflict of Interest:** Mehmet Canpolat is Editorial Board Member in the Journal of Pediatric Academy. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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