# Cockayne Syndrome

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## Background

Cockayne syndrome is a rare autosomal recessive disease, with heterogeneous presentation which involves many organ systems and is characterized by failure to thrive, microcephaly, pigmentary retinopathy, and photosensitivity. The face of the patients resembles the face of the birds. There are 3 subtypes of this disorder. Type I, or classic Cockayne syndrome, presents in childhood with characteristic facies and somatic features that occur late in the first decade of life. Type II, or severe congenital or neonatal form, presents at birth with accelerated facial and somatic features. Type III Cockayne syndrome has the mildest symptoms of the three types and appears later in childhood. Patients with Cockayne syndrome type I typically have progressive neurologic degeneration with death occurring by the second or third decade of life, while patients with type II of the disease mostly do not survive the first decade of life.

## Pathophysiology

A DNA repair defect is a prominent feature of Cockayne syndrome. Cockayne syndrome, xeroderma pigmentosa, and trichothiodystrophy are three distinct syndromes with cellular sensitivity to ultraviolet (UV) irradiation. These syndromes arise from mutations of genes critical for nucleotide-excision repair and RNA transcription. At least 28 genes are involved in the nucleotide excision repair pathway. The pathway is involved in protection against UV-induced DNA damage. Cells with a defective DNA repair mechanism are sensitive to UV light. Decreased DNA and RNA synthesis, increased sister chromatid exchanges, and increased chromosomal breaks may occur.

Despite the photosensitivity and DNA repair defect, and unlike xeroderma pigmentosa Cockayne syndrome is not associated with skin cancer.

## Epidemiology

Cockayne syndrome is rare throughout the world. No racial predilection is reported. No sexual predilection is described and the male-to-female ratio is equal.

## History

Patients with Cockayne syndrome usually appear normal at birth, but eventually, they present with a typical facial appearance of a narrow face and a beaked nose. Mental retardation, microcephaly, and growth failure become evident over time. Photosensitivity and progressive worsening neurologic signs and symptoms of ataxia and quick jerky movements are also noted. In type I the signs become gradually more pronounced during the first decade of life, but in CS-II, severe

developmental delays are evident from early postnatal days, and the facies may become characteristic by 2 years of age.

**Physical Exam**

Microcephaly, a thin nose, and large ears give the patient a Mickey Mouse appearance. Patients may be cachectic. Photosensitive eruption with erythema and scale may be observed. Affected areas show hyperpigmentation, telangiectasia, and atrophy. Subcutaneous lipoatrophy results in sunken eyes and an aged progeric appearance. Microcephaly, short stature, long limbs with joint contractures, large hands and feet, kyphosis, and osteoporosis may be observed. Dental caries may be present.

Salt and pepper retinal pigment, miotic pupils, cataracts, optic atrophy, corneal opacity, and nystagmus may be seen in ophthalmologic exam. Vision is preserved.

**Neurologic findings**

Intracranial calcifications and diffuse demyelination of the central nervous system and the peripheral nerves result in progressive neurologic deterioration, such as ataxia, tremors, and cog wheeling. Mental retardation may be noted. Progressive sensorineural deafness may occur.

**Diagnosis**

Diagnosis is based on detection of the specific TCR defect that can be identified using a radioactive assay in cultured fibroblasts that measures the recovery of RNA synthesis after UV irradiation. This DNA repair test is a decisive tool for the diagnosis of CS.

**Differential Diagnoses**

- Bloom Syndrome (Congenital Telangiectatic Erythema)
- Hartnup Disease
- UV-sensitive syndrome
- Xeroderma Pigmentosum

**Laboratory Studies**

Laboratory studies are mainly useful to eliminate other disorders. For example, skeletal radiography, endocrinologic tests, and chromosomal breakage studies can help in excluding disorders included in the differential diagnosis.

Amniotic fluid cell culturing can be used to demonstrate that fetal cells are deficient in RNA synthesis after UV irradiation.

**Imaging Studies**

Brain imaging reveals diffuse hypomyelination of the cerebral white matter, calcifications in the putamen, and vermian atrophy. Cortical atrophy is also a nonspecific finding. Patients with early-onset disease display more severe hypomyelination and prominent calcifications in the sulcal depth of the cerebral cortex, but atrophy is less severe in late-onset patients. On proton MR spectroscopy, lactate is detected and Cho and NAA values are decreased.

**Medical Care and Prognosis**

Medical care for Cockayne syndrome patients includes photoprotection with sunscreens and clothing.The prognosis for Cockayne syndrome is poor, with death occurring in the second or third decade of life. A genetic counselor should educate the parents of the Cockayne syndrome patient.

**Keywords:** Cockayne Syndrome;Leukodystrophy