Review article

# Cockayne syndrome. An update.

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## Abstract

Cockayne's syndrome is a rare heterogeneous autosomal recessive disorder with poor genotype-phenotype correlation. The basic underlying abnormality in CS is defective transcription-coupled repair of DNA whereas the global genome repair pathway of nucleotide-excision repair is normal. Clinically the spectrum of CS spans from classical type (CS type 1, CKN1, CSA), a more severe form with symptoms present at birth (CS type 2, CSB, also known as cerebro-oculo-facial syndrome and Pena-Shokeir type II syndrome), a milder form (CS type 3), and xeroderma pigmentosum-Cockayne syndrome (XP-CS). However, CS type 1 and CS type 2 are the major phenotypes. The cardinal features of CS are growth failure, premature aging, and pigmentary retinal degeneration along with a number of nonspecific clinical findings. The definite diagnosis requires assay of DNA repair in skin fibroblasts or lymphoblasts. Prenatal diagnosis is also possible at 16-18 weeks of gestation. There is progressive downhill course with premature death before adulthood. Besides genetic counselling a multidisciplinary approach is required.

## Introduction

Cockayne's syndrome (CS); also called *Neill-Dingwall syndrome*, *progeria-like syndrome* and *progeroid nanism*; belongs to a group of inherited disorders with heterogeneous clinical features which have *in vitro* or *in vivo* cellular hypersensitivity to damage by certain physical or chemical agents. These diseases include xeroderma pigmentosum (XP), Cockayne syndrome, trichothiodystrophy (TTD), Bloom syndrome, Fanconi anemia, dyskeratosis congenita, basal cell nevus syndrome, ataxia-telangiectasia, and familial melanoma with dysplastic nevi.[1] Clinically, the cutaneous, ocular, nervous, immune, hemopoietic, skeletal, or gastrointeinal systems are affected. Some are associated with increased incidence of neoplasia. There may be a progressive deterioration of body functions. The cellular hypersensitivity is helpful in the diagnosis, understanding the pathogenic mechanisms and devising therapeutic or prophylactic intervention. The molecular basis of the cellular hypersensitivity has been explored in some of these disorders. This review focuses on the clinical features and laboratory abnormalities of CS.

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## History

The syndrome was described first by Edward Alfred Cockayne, a British pediatrician in 1936.[2] His patient had cachectic dwarfism, deafness, and pigmentary retinal degeneration with a characteristic "salt and pepper" appearance

of the retina. The skin had photosensitivity without the excessive pigmentary abnormalities seen in XP. There was marked loss of subcutaneous fat, resulting in a "wizened" appearance with typical "bird-headed" facies and prominent "Mickey Mouse" ears. Other ocular findings included cataracts and optic atrophy. Later, Catherine M. Neill and Mary M. Dingwall[3] reported similar cases in 1950. Since then many cases have been recognized and published in the literature. A review published in 1992 described 140 cases reported in the literature.[4]

**Prevalence**

The exact prevalence is not known as essentially all cases have been reported as single cases or family reports. The figure generally used for rare diseases is 1/100,000 but CS occurs even less frequently than this.[5] The reported frequency in United States[6] is less than 1/250,000. CS has been reported to be more common in isolated or inbred communities.

CS affects all races without any sex predilection.[6] As it is a genetic disorder the manifestations may be delayed until early childhood.

**Etiology**

CS is an autosomal recessive disorder. The basic defect is the slow transcription-coupled DNA repair whereas the global genome repair pathway of nucleotide-excision repair mechanism is intact.[7]

***Complementation groups in CS*** [5,6,8]

On the basis of underlying genetic, CS has two complementation groups, CS type 1 (CSA) and CS type 2 (CSB) due to defect in *ERCC8* and *ERCC6* genes, respectively.

**Table 1** The underlying molecular genetic defects in Cockayne's syndrome [5]

| | *CKN1, CSA* | *CS type 2, CSB* |
|---|---|---|
| Gene | CSA gene *ERCC*8 | CSB gene *ERCC*6 |
| Gene locus | 5<br>MIM 216400 | 10q11<br>MIM 133540 |
| Frequency | 25% of cases | 75% of cases |
| Product | Cockayne syndrome WD-repeat protein (CSA protein)<br>396 amino acids<br>44 kDa | Excision repair protein ERCC6 (CSB protein)<br>1349 amino acids |
| Types of mutation | Point mutation<br>Deletion of *ERCC8* | Missense mutation<br>Insertion deletion of *ERCC6* |

ERCC=excision repair cross-complementig group, MIM=Mendelian inheritance in man

Both *ERCC8* and *ERCC6* transcribe to two proteins CSA and CSB, respectively. Wild CSA and CSB proteins remove the stalled polymerase in such a way that the lesion becomes accessible to repair enzymes. The mutated proteins are deficient in their function. However, the genotype-phenotype relation is not absolute. The involved genes, their respective loci and product are shown in **Table 1**.

***Cellular and molecular genetic overlap in CS, XP, and TTD*** [8,9]

CS, XP, and TTD share common etiology i.e. defective nucleotide excision repair (NER). It is a complex mechanism to repair DNA and hence to protect the genome against injury induced by numerous mutagenic and carcinogenic agents

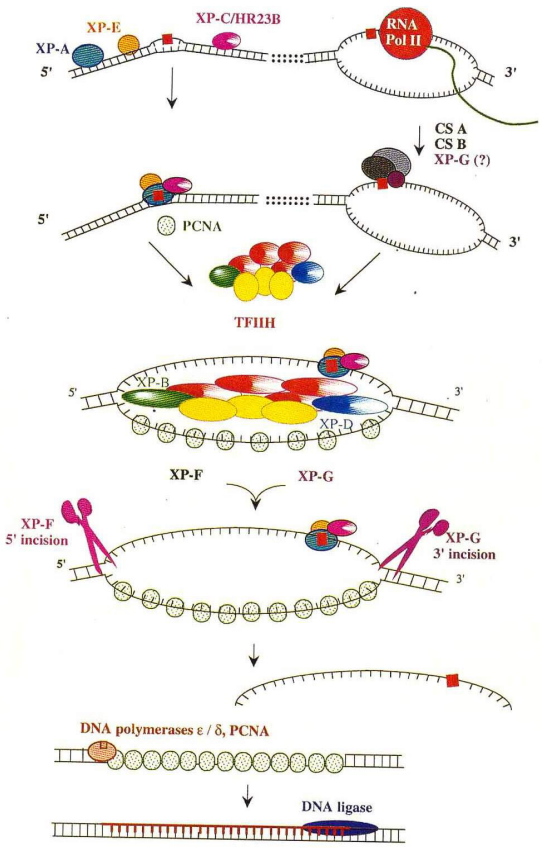


**Figure 1** Model showing two pathways of NER i.e. global genome repair (left side) and transcription-coupled repair (right side) [10].

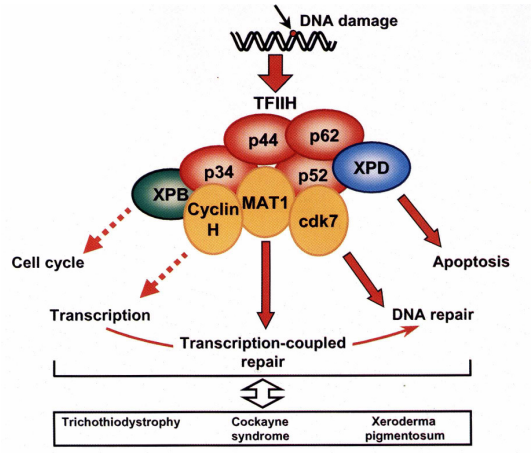


**Figure 2** Suggested hypothesis of TFIIH dysfunction can lead to XP, CS and TTD [10].

e.g. photoproducts, chemical-produced adducts, intrastrand crosslinks etc. Different steps involved are, a) recognition of DNA lesion, b) removal of the damaged oligonucleotide, c) gap filling by DNA synthesis, and d) ligation.

NER further comprises of two pathways. One is the more rapid, transcription-coupled repair (TCR) of expressed genes, targeted to the transcribed strand. The other is slower, global genome repair (GGR) of DNA, which includes repair of the nontranscribed strand of expressed genes and the inactive chromatin.

**Figure 1** shows both pathways of NER. In GGR (*left part*), the complex XP-C/HR233B binds to DNA lesions and attracts XP-A, RPA (ssDNA binding protein) and then TFIIH (*recognition of DNA lesion*). XP-E protein facilitates the identification of lesions which are poorly recognized by XP-C/HR233B e.g. cyclobutane pyrimidine dimers. Demarcation of the lesions is carried out by XP-B and XP-D (two helicases) of TFIIH followed by sequential cleavage by two structure-specific nucleases XP-G (on 3' side) and ERCC1-XP-F (on 5' side) [*removal of damaged oligonucleotides*]. After removal of an oligonucleotide containing the lesion, DNA synthesis occurs using either polymerase δ or ε in the presence of PCNA and RF-C complexes as processitivity factors (*gap filling by DNA synthesis*). The final step is *ligation* of the newly synthesized DNA patch to parental strand by DNA ligase I.[10]

TCR differs from GGR in the initial step i.e. recognition of lesion only (*right half*). On damaged templates, RNA polymerase II is blocked by the lesion inducing signal for TCR. Proteins CSA, CSB, and possibly

XP-G and TFIIH displace the stalled RNA poly II from the lesion. Now the lesion becomes accessible for further repair in the same way as for GGR.[10]

Transcription and DNA repair are two closely associated processes. TFIIH is a complex of 9 proteins which has dual role in transcription and repair. It inhibits cell cycle and transcription but induces TCR, DNA repair, or apoptosis after genome damage. It is speculated that CS, XP, or TTD are the consequences of TFIIH dysfunction. Mutations in one of the two DNA repair genes in TFIIH may lead to three different human disorders: a) XP (the skin cancer-prone syndrome), b) CS or TTD alone, and c) CS- or TTD-associated with XP in the same patient (**Figure 2**). It is hypothesized that some of DNA-repair deficient patients may also have transcription deficiency. The same gene defect can result in apparently identical cellular phenotypes related to DNA repair deficiency, yet give rise to completely different clinical features.

***Cellular hypersensitivity***

Like XP, cultured cells (fibroblasts or lymphocytes) from patients with CS are hypersensitive to UV-induced inhibition of growth and colony-forming ability.[11] Host cell reactivation of UV-damaged adenovirus or plasmids is reduced, although to a lesser extent than in XP.[12] Increased mutation frequency has been reported in circulating lymphocytes from two donors with CS.[13]

***Chromosome abnormalities***

Chromosome karyotype and sister chromatid exchange frequency is usually normal in untreated cells but increase in sister chromatid exchanges and a delayed recovery of chromosome damage is reported after UVR exposure.[11,14,15]

**Table 2** compares the laboratory characteristics and main clinical features in the three NER syndromes [10].

| | *XP* | *CS* | *TTD* |
|---|---|---|---|
| UV sensitivity | +, ++ | + | + |
| Residual UDS | 5%-50% | 15-50% | WT |
| TCR | ↓ except XP-C | ↓ | ↓ |
| GGR | ↓ | WT | ↓ |
| Photosensitivity | ++ | +[a] | +[a] |
| Skin cancer | ++ | -[b] | -[b] |
| Progressive mental degeneration | +/- | + | + |
| Neuronal loss | +/- | + | + |
| Neurodysmyelination | - | + | + |
| Thin facies | - | + | + |
| Growth defect | +/- | + | + |
| Hypogonadism | +/- | + | + |
| Brittle hair and nails | - | - | + |
| Ichthyosis | - | - | + |

GGR=global genome repair, TCR=transcription-coupled repair, UDS=unscheduled DNA synthesis, WT=wild type (control level), +=present, ++=markedly present, +/-=sometimes present, ↓=reduced, a=patients with CS and TTD may have no photosensitivity, b=skin cancer may be present in XP/CS or XP/TTD overlap

**Pathophysiology**

Pathologic studies reveal diffuse and extensive demyelinating in the central and peripheral nervous systems. Patients demonstrate pericapillary calcifications in the cortex and basal ganglia at an early age.[6] Severe neuronal loss in the cerebaral cortex and cerebellum also occurs. These changes correlate with the physiologic changes of skin.

**Clinical features** [4,5,6]

With elucidation of molecular genetic defects, it has been recognized that CS is not a single phenotype but it spans a spectrum

that comprises: CS type 1, the classical form; CS type 2, a more severe form with symptoms present at birth, also called connatal CS (previously called cerebro-oculo-facial [COFS] syndrome and Pena-Shokeir type 2 syndrome; CS type 3, a milder form; and xeroderma-pigmentosum-Cockayne syndrome (XP-CS). CS type 1 and CS type 2 are the two well-accepted types.

*CS type 1 (classical, CNK1, CSA)*

Birth weight, length and head circumference are normal. However, within the first two years growth and development become abnormal. There is delayed psychomotor development, poor feeding, photosensitive rashes and cataract. By the time the disease becomes fully manifest, height, weight, and head circumference are far below the fifth percentile. The characteristic appearance of a child with CS is a cachectic dwarf with thinning of the skin and hair, sunken eyes, and a stooped standing posture (**Figure 3**). Different clinical signs and symptoms reported in CS are enlisted in **Table 3**. Progressive impairment of vision (due to cataracts and pigmentary retinopathy), sensorineural deafness, hypertension, joint

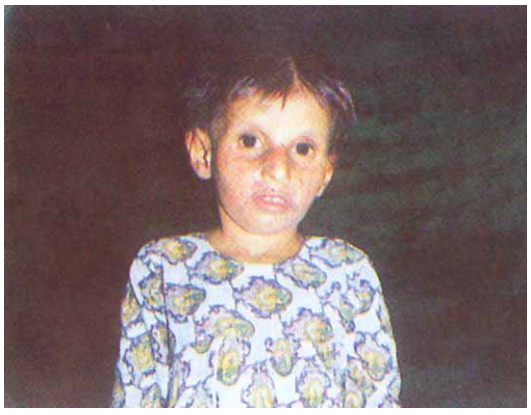

**Figure 3** A girl showing typical facies of CS with sunken eyes, beaked nose, large ears, and freckles over face.

**Table 3** Clinical signs/symptoms reported in Cockayne syndrome [4,5,6].

- *Neurologic*
  Increased tone/spasticity
  Hyper- or hyporeflexia
  Abnormal gait or inability to walk, ataxia
  Incontinence
  Tremors
  Abnormal speech or absence of speech, seizures
  Weak cry/poor feeding
  Muscle atrophy
  Behavioral abnormality
  Seizures
- *Dermatologic*
  Photosensitivity (~75%)
  Malar rash
  Xerosis
  Mottled pigmentation and atrophic scars
  Loss of subcutaneous fat
  Premature aging
  Anhidrosis
  Thin, dry hair
- *Ophthalmologic* [16]
  Pigmentary retinal degeneration/retinitis pigmentosum (develops late) [~55%]
  Cataract (before 3 years)[~36%]
  Miotic pupils
  Farsightedness
  Decreased or absent tears
  Strabismus
  Nystagmus
  Photophobia
  Narrowed retinal arterioles
  Microcornea
  Iris hypoplasia
  Microphthalmia.
  Optic atrophy
- *Ears*
  Sensorineural deafness (mild-moderate) [~66%]
- *Dental*
  Caries (~86%)
  Absent or hypoplastic teeth
  Delayed eruption of deciduous teeth
  Malocclusion
- *Endocrinal*
  Undescented testes
  Delayed/absent sexual maturation
  Infertility
- *Musculoskeletal*
  Skeletal dysplasia
  Relatively long limbs
  Contractures of hips, knees, ankles

- *Gastrointestinal*
  Elevated liver function tests
  Hepatosplenomegaly
- *Renal* [17]
  Hypertension
  Decreased creatinine clearance
- *Other*
  Reduced immunity to infections

contractures and ataxia lead to severe disability. However, CS is not associated with an increased incidence of neoplasia. Death typically occurs in the first or second decade as a result of pneumonia and other respiratory infections. The mean age of death is 12 years, but survival into third decade has been reported.

*CS type 2 (CSB)*

Also called 'connatal' CS, is the severe form of syndrome in which growth failure is evident at birth and little or no postnatal neurological development occurs. Congenital cataracts or other structural anomalies of the eye are reported in 30%. Patients have arthrogryposis or early contractures joints and spine (kyphosis, scoliosis). Patients typically die by the age of 7 years. This group overlaps clinically with two other genetic disorders named, the cerebro-oculo-facial syndrome (COFS) and Pena-Shokeir type II syndrome. A mutation in the *ERCC6* gene has been reported in COFS. It is now recognized that patients previously labeled to have COFS or Pena-Shokeir type II syndrome, who have molecular or biochemical evidence of *ERCC8* or *ERCC6* mutations or characteristic DNA repair abnormalities, should be diagnosed as having Cockayne syndrome type 2.

*CS type 3*

Before the discovery of molecular defects of CS, a few cases with some features of CS but with essentially normal growth and cognitive development, or late onset, were reported.[18] These have been categorized as CS type 3. The molecular defect in DNA repair or protein complementation has not been documented. In a single case clinically resembling late-onset CS, an insertional deletion of chromosome 10q21.1 has been reported.

*Xeroderma pigmentosum–Cockayne syndrome complex*

The correlation between genotype, cellular phenotype, and clinical phenotype is not absolute. A number of patients with CS have been found to have, in addition, clinical features of XP. These features include freckling on sun-exposed skin and cutaneous neoplasms. Cells from these XP/CS patients have reduced DNA excision repair characteristic of XP. Clinically, these patients may be distinguished from XP patients with neurologic abnormalities by the presence of the CS features of pigmentary retinal degeneration, calcification of the basal ganglia, normal-pressure hydrocephalus, and hyperreflexia. Cells from patients with this complex have been assigned to XP-B, -D, and -G, complementation groups. The De-Sanctis-Cacchione[19] variant of xeroderma pigmentosum includes some features of CS such as mental retardation, spasticity, short stature, and hypogonadism, but without skeletal dysplasia, the facial phenotype of CS, or CNS demyelination and calcifications.

**Diagnosis** [4,5,6]

The characteristic features of syndrome may not be evident and the diagnosis may be delayed for years. Poor psychomotor

development, emergence of a typical abnormality of CS e.g. blindness, deafness, or extreme photosensitivity make parents visit a physician. No consensus guidelines have been developed whether CS should be diagnosed exclusively on the basis of clinical criteria, cellular phenotype, genetic phenotype, or a combination of the three. The syndrome is diagnosed by clinical findings in classical cases and in non-classical cases by assay of DNA repair in skin fibroblasts or lymphocytes. Such testing is available in a few clinical laboratories.

***Clinical Diagnosis***

*Classical Cockayne syndrome (CS type 1)*

The suggested diagnostic criteria for CS1 are given in **Table 4**. CS type 1 is suspected in an older child when both major and three minor criteria are present or in an infant or toddler when both major and one minor criterion along with abnormalities of DNA repair are present.

*Connatal Cockayne syndrome (CS type 2)*

CS type 2 is suspected in infants with growth failure at birth with little postnatal increase in height, weight, or head circumference.

1. Little or no postnatal neurological development.
2. Congenital cataracts with other structural defects of the eye (microphthalmos, microcornea, iris hypoplasia).

***Laboratory findings*** [5,6]

Molecular genetic testing includes the following test:

*UV survival curve test*

CS cells are abnormally sensitive to ultraviolet radiation. Typically half to one-fourth as much as UVR kills majority of CS cells (fibroblasts or lymphoblasts) as compared to normal cells.

**Table 4**: Suggested diagnostic criteria for CS type 1 [5]

*Major criteria*

1. Height and weight below fifth percentile for age and sex.
2. Developmental delay (absence or delayed nervous system milestones e.g. ability to speak or walk)

Minor criteria

1. Cutaneous photosensitivity with or without thin or dry skin or hair.
2. Sensorineural deafness.
3. Pigmentary retinopathy and/or cataract.
4. Dental caries.
5. A characteristic physical appearance of cachectic dwarfism with thinning of the skin and hair, sunken eyes, and a stooping posture, large for head size ears 'Mickey-mouse ears,' small chin with prominent, pointed 'birdlike' nose, decreased facial subcutaneous adipose tissue, microcephaly, an aged or wizened facial appearance.
6. Demyelinating peripheral neuropathy (~ 75%) diagnosed by electromyography, nerve conduction testing, and/or nerve biopsy.
7. Characteristic radiographic findings of thickening of the calvarium, sclerotic epiphyses, vertebral and pelvic abnormalities.

*RNA synthesis inhibition assay*

This test assesses the transcription-coupled DNA repair. CS cells along with control (cells from a normal person) are exposed to UVR. RNA synthesis in CS cells is much lower than normal cells due to their inability to repair UVR-induced damage.

*Complementation group testing*

This test identifies whether a patient belongs to CSA or CSB, seen in 25% and 75% of patients, respectively. When fused together and exposed to UVR, cells from different

groups having different genetic defect will complement each other, showing enhanced DNA repair. Currently complement testing is more of research interest than of immediate value to patient. Such testing may be helpful, in future, to plan protein therapy or gene therapy that is defective in a patient.

*Mutation analysis*
This test is also of research interest. This detects the type of mutation and the mutated genes in a family.

Many other tests may be helpful in the management. CT scan of brain shows characteristic brain structural abnormalities including calcium deposits in the basal ganglia and normal pressure hydrocephalus (ventricular enlargement without obstruction). Magnetic resonance imaging (MRI) of the brain shows atrophy and dysmyelination of the cerebrum and cerebellum. The electroencephalogram may be abnormal, and x-ray examination may show thickened skull and microcephaly. Other tests may show sensorineural deafness, neuropathica electromyogram, and slow motor nerve conduction velocity. Bone age is usually normal.

**Prenatal Diagnosis**
Prenatal diagnosis has been reported by analysis of ultraviolet light sensitivity and DNA repair in fetal cells obtained by amniocentesis at 16-18 weeks gestation. This test is still of research interest and not offered clinically.[21]

**Differential diagnosis** [5,6]
The differential diagnosis of CS depends on the presenting features of the particular patient. Abnormalities that suggest alternative diagnoses are congenital anomalies of the face, limbs, heart, or viscera, recurrent infections other than otitis media or respiratory infections; metabolic or neurologic crises; hematologic abnormality e.g. anemia, leuopenia; or malignancy of any kind.

- Growth failure is a feature of many chromosomal, endocrine, metabolic, or gastrointestinal disorders including malnutrition. Syndromes with profound growth failure e.g. Brachmann-de Lange, Duboitz, Hallerman-Streiff, Rubinstein-Taybi, Russel-Silver, Seckel, and Wiedemann-Rautenstrauch etc. can usually be excluded on the basis of physical appearance.
- In cases with photosensitivity or thinning of the skin and hair, the differential diagnosis includes xeroderma pigmentosum, Bloom syndrome, Rothmund-Thompson syndrome, and the premature aging syndromes e.g. progeria, Werner syndrome etc.
- Barring Pelizaeus-Merabacher disease, growth failure does not occur in most leukodystrophies.
- The presence of calcification on brain imaging might suggest congenital infections e.g. rubella or toxoplasmosis.

**Management** [5,6]
The management issues are, comprehensive baseline evaluation and then serial monitoring; symptomatic care; and genetic counseling.

Baseline evaluation includes measurement of growth, development assessment, dental

evaluation, dermatologic assessment, ophthalmologic evaluation possibly including electroretinogram, audiologic evaluation including audiogram, brain MRI, CT scan, EMG to document the presence of demyelinating neuropathy, laboratory studies to assess renal and hepatic function, testing for diabetes mellitus or disorders of calcium metabolism, and skeletal radiographs to document the skeletal dysplasia. Patients should be followed up and yearly assessed for known potential complications e.g. hypertension, renal or hepatic dysfunction, declining vision and hearing.

Symptomatic care should focus on an individualized education program, assistive devices, and safety in the home for developmental delay and gait disturbances. Regular physiotherapy may help prevent contractures and maintain ambulation. Feeding tube may be indicated, if feeding is unsatisfactory, to prevent malnutrition. Aggressive dental care, use of sunscreens and avoidance of excessive sun exposure are advisable. Specific problems may be evaluated and treated by appropriate specialists e.g. pediatricians, dermatologists, ophthalmologists, otolaryngologists, audiologists, clinical geneticists and rehabilitation therapists. These children may benefit from special education including sign language training, and from devices such as ankle and foot orthotics to assist walking, and hearing aids. From the dermatologist viewpoint, children with CS should avoid sun exposure though not such strict protection is required as in XP. Additional protection may be acquired by use of protective clothing and sunblocks with SPF $\geq$ 15.

CS children, despite their many problems, are affectionate and cheerful. Nonetheless, they need more attention because of their physical and mental handicap. Families of children with CS are under great stress due to the need to provide extra attention, medical emergencies due to complications of CS, and financial burden. There is an educational, advocacy, and support organization[22] for helping patients with CS and their families: The Share and Care Cockayne Syndrome Network Box 552 Stanleytown, VA 24168Tel: 540-629-2369;
FAX: 540-647-3728
E-mail: cockayne@kimbanet.com

It is also important to provide the patient and family with information on the nature, inheritance, and other implications of the disease to help them make informed medical and personal decisions. The parents of an affected child are both obligate carriers of an abnormal gene. The sibs of a proband have a 25% chance of being affected, a 50% chance of being an 'unaffected carrier', and a 25% chance of being normal. As this is a very rare disorder, carriers can be counseled that their chance of meeting another in the general population is on the order of 1/5,000, and the chance of having an affected child is one-quarter of that i.e. 1/20,000. Carrier testing can only be performed by DNA analysis. Reproduction has not been reported in any individual with CS.

**Prognosis**

Patients with CS suffer a lot of morbidity including neurological, dermatological, ophthalmologic, dermatological, and otic complications. The average life span in CS is reported to be 12 years, though, the

severity of the genetic damage in the affected individual and the food intake are two important determinants. The oldest CS patient is reported to be of 30's. They end up with premature death due to respiratory tract infection.

## Future prospects

It is hoped that the understanding of genes, mutations and testing methodologies will improve in future. As medical genetics and bioengineering advances, gene therapy or treatment with their products remains another ray of hope for CS patients. DNA of patients (extracted from leukocytes) should be stored for future use.

## References


1. Kraemer KH. Heritable diseases with increased sensitivity to cellular injury. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in general medicine*, *5th edn*. New York: McGraw-Hill; 1999. p. 1848-62.
2. Cockayne EA. Dwarfism with retinal atrophy and deafness. *Arch Dis Child* 1936; **11**: 148.
3. Neil C, Dingwall MM. A syndrome resembling progeria. A review of two cases. *Arch Dis Child* 1950; **11**: 213-21.
4. Nance MA, Berry SA, Cock S. Review of 140 cases. *Am J Med* 1992: **42**: 68-84.
5. Nance MA. Cockayne syndrome. *Gene Reviews* [serial online] 2000. Available from: URL: htt:www.geneclinics.org/servlet/access…/details/htm.
6. Carter SM, Gross SJ. Cockayne syndrome. *eMed J* [serial online] 2002; **3**(4): [11 screens]. Available from; URL: htt://www.emed.com/cgi-bin/foxweb.exe/screen.
7. Venema J, Mullenders LHF, Natarajan AT *et al.* The genetic defect in Cockayne syndrome is associated with a defect in repair of UV-induced DNA damage in transcriptionally active DNA. *Proc Natl Acad Sci USA* 1990; **87**: 4707-11.
8. Cleaver JE, Thompson LH, Richardson AS, States JC. A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *Hum Mutat* 1999; **14**: 9-22.
9. Le Page F, Kwoh EE, Aurutskaya A *et al*. Transcription-coupled base excision repair and mutation avoidance at 8-oxoguanine requirement for XPG, TFIIH, and CSB and implication for Cockayne syndrome. *Cell* 2000; **101**: 159-71.
10. Itin PH, Sarasin A, Pittelkow MR. Trichthiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol* 2001; **44**: 891-920.
11. Marshall RR, Arlette CF, Harcourt SA, Broughton BA. Increased sensitivity of cell strains from Cockayne's syndrome to sister-chromatid-exchange induction and cell killing by UV light. *Mutat Res* 1980; **69**: 107-12.
12. Parris CN, Kraemer KH. Ultraviolet-induced mutations in Cockayne syndrome cells are primarily caused by cyclobutane dimmer photoproducts while repair of other photoproducts is normal. *Proc Natl Acad Sci USA* 1993; **90**: 7260-9.
13. Norris PG, Arlette CF, Cole J *et al*. Abnormal erythemal response and elevated T lymphocyte HRPT mutant frequency in Cockayne's syndrome. *Br J Dermatol* 1991; **124**: 453-60.
14. Seguin LR, Tarone RE, Liao KH, Robbins JH. Ultraviolet light-induced chromosomal aberrations in cultured cells from Cockayne syndrome and complementation group C xeroderma pigmentosum patients: lack of correlation with cancer susceptibility. *Am J Hum Genet* 1988; **42**: 468-75.
15. Price FM, Parshad R, Tarone RE, Sanford KK. Radiation-induced chromatid aberrations in Cockayne syndrome and xeroderma pigmentosum group C fibroblasts in relation to cancer predisposition. *Cancer Genet Cytogenet* 1991; **57**: 1-10.
16. Traboulsi EI, De Becker I, Maumenee IH. Ocular findings in Cockayne syndrome. *Am J Ophthalmol* 1992; **114**: 579-83.
17. Higginbottom MC, Griswold WR, Jones KL *et al.* The Cockayne syndrome: an evaluation of hypertension and studies of renal pathology. *Pediatrics* 1979; **64**: 929-34.
18. Colella S, Nardo T, Mallery D *et al*. Alteration in the CSB gene in three Italian patients with severe form of CS but without

clinical photosensitivity. *Hum Mol Genet* 1999; **8**: 935-41.
19. Czeizel AE, Marchalko M. Cockayne syndrome type III with high intelligence. *Clin Genet* 1995; **48**: 331-3.
20. Colellia S, Nardo T, Botta E *et al*. Identical mutations in CSB gene associated with either CS or DeSanctis-Cacchione variant of xeroderma pigmentosum. *Hum Mol Genet* 2000; **9**: 1171-5.
21. Cleaver JE, Volpe JP, Charles WC, Thomas GH. Prenatal diagnosis of xeroderma pigmentosum and Cockayne syndrome. *Prenat Diagn* 1994; **14**: 921-8.
22. The share and care Cockayne syndrome network: http//members.aol.com/DBBusch/shareandcarehome.html