



# A Unique Presentation of Cockayne Syndrome with a Pure Neurological Phenotype

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## Abstract

Cockayne Syndrome (CS) is a genetic disorder characterized by growth retardation, neuromotor disabilities, impaired vision, hearing, intellectual deficit and dermatological abnormalities. Its incidence is estimated to be 1 in 250,000 live births. It occurs due to defective DNA repair by nucleotide excision repair. There are four different types of CS - a) the classical form- CS type I characterized by progressive symptoms, apparent after one year of age; b) Congenital form- CS type II, symptoms apparent at birth; c) CS type III presents in later childhood; d) fourth type- Xeroderma Pigmentosa-Cockayne Syndrome (XP-CS) combining the manifestations of both diseases.

**Keywords:** Cockayne syndrome; Neurological; Atypical; Failure to thrive; Growth retardation

## Case Presentation

A 1 year-10-month-old girl was brought with concerns of developmental delay noticed since 8 months of age. She attained neck control by 3 months, was able to roll over by 6 months, and sit with support by 7 months. After that, there was a delay in attainment of subsequent milestones. She was able to sit without support by 1 year of age, stand with support by 1.3 years. She was not able to stand or walk without support, did not have a pincer grasp, was not able to say disyllables and was unable to wave bye-bye. She was the first-born child to non-consanguineous parents and had a smooth perinatal transition with a birth weight of 2.5 kg. There was no significant family history of note. She was found to have decreased weight gain and growth retardation from the later part of her infancy. Her mother also complained of stereotypic repetitive voluntary swaying movements of trunk forward and backward since 1 year of age. She did not have any seizures, weakness, difficulty in hearing or vision. There was no unsteadiness noticed while sitting or standing. There was no history of skin ulcers, photosensitive rash or pigmentation abnormalities and no peculiar body odor was noted by her mother. Her anthropometry revealed severe underweight for age (8.2 kg; <-3Z score), severe stunting (70 cm; <-3Z score), normal weight for height (0 Z to 1 Z) and microcephaly (41 cm). General examination revealed hypopigmented hair, flat nasal bridge, and normal dentition without any cataract or neurocutaneous markers. Neurological examination revealed bilateral lower limb spasticity and variable tone in upper limbs, brisk deep tendon reflexes, left convergent esotropia and a voluntary trunk swaying behavior when placed in sitting position. Other systemic examination was non-contributory. Ophthalmological and otorhinolaryngological examinations were within normal limits. The initial differential diagnoses considered were inborn errors of metabolism like phenylketonuria, Vitamin B12 deficiency or leukodystrophies like spastic paraparesis. Initial hematological and biochemical investigations were within normal limits (Table 1). Magnetic Resonance Imaging (MRI) of the brain was normal. Blood phenylalanine levels were normal and Tandem Mass Spectroscopy (TMS) did not reveal any abnormality. A clinical exome sequencing was done, which revealed a homozygous missense variation in exon 7 of the ERCC8 gene (chr5: g.60902494T>A; Depth: 54x) that resulted in the amino acid substitution of Leucine for Isoleucine at codon 189 (p.Ile189Leu; ENST00000265038.10), confirming the diagnosis of Cockayne syndrome-A. Appropriate genetic counseling was given to the parents.

Cockayne Syndrome (CS), is a genetic disorder characterized by growth retardation, neuromotor disabilities, impaired vision, hearing, intellectual deficit and dermatological abnormalities [1]. Its incidence is estimated to be 1 in 250,000 live births [2]. It occurs due to defective DNA repair by Nucleotide excision repair. There are four different types of CS- a) the classical form- CS type I characterized by progressive symptoms, apparent after one year of age; b) Congenital form- CS type II, symptoms apparent at birth; c) CS type III presents in later childhood; d) fourth type-

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Received Date: 28 Sep 2022

Accepted Date: 13 Oct 2022

Published Date: 17 Oct 2022

### Citation:

Chidambaram AC, Vidhyasagar K, Dinesh Babu RM, Vijayagopalan DK, Manga HS, Sagayaraj B. A Unique Presentation of Cockayne Syndrome with a Pure Neurological Phenotype. *Ann Pediatr Res.* 2022; 6(2): 1069.

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**Table 1:** Investigations of the index case.

Investigation	Patient Value	Reference Range
Hemoglobin (g/dL)	11.3	11.5-14.5
Total leukocyte count (x10 <sup>9</sup> /L)	9.39	4.5-11
Platelet count (x 10 <sup>9</sup> /L)	232	150-450
Total Bilirubin (mg/dL)	0.1	0.6-1.2
Direct bilirubin (mg/dL)	0.03	
Alanine transaminase (U/L)	17	5-40
Aspartate transaminase (U/L)	39	5-40
Creatine phosphokinase (U/L)	78	10-120
Free T3 (pg/mL)	6.47	5.0-12.0
Free T4 (ng/dL)	1.63	0.7-2.0
Thyroid stimulating hormone (mIU/mL)	2.84	0.5-5.0
Vitamin B12 (pg/mL)	291	200-800
Bicarbonate (mEq/L)	22	22-26
Lactate (mmol/L)	0.9	<2
Ammonia (µg/dL)	40	15-45
Serum Phenylalanine (mg/dL)	4.3	<10
Brainstem evoked response audiometry	Normal	
Tandem Mass spectroscopy	Negative	

Xeroderma Pigmentosa-Cockayne Syndrome (XP-CS) combining the manifestations of both diseases [3].

CS involves myriad of clinical manifestations involving the auditory, ophthalmological, dermatological, neurological, musculoskeletal, cardiovascular, gastrointestinal and renal systems. Facial dysmorphism in the form of wizened facies, sunken eyes, and large ears, thin pointed nose, and small chin are commonly noted [4]. There is severe Failure to Thrive (FTT) and CS patients are often termed “cachectic dwarfs”. High tone Sensorineural Hearing Loss (SNHL) is one of the cardinal manifestations of CS [5]. Among the ophthalmological complications, cataracts, corneal opacification and pigmentary retinopathy have been often described [5-7]. Photosensitivity, wrinkled and aged skin constitute the dermatological phenotype of CS [8]. Cardiomyopathy, hypertension and aortic root dilatation are infrequently described. Our patient did not manifest any of these systemic features, but had severe FTT.

The neurological manifestations of CS contribute to significant morbidity of the disease. Affected individuals have severe microcephaly, which begins in later part of infancy and is present in all individuals after the age of two years [6,8]. Most children with CS have delayed attainment of milestones, leading to motor dysfunction, difficulty in ambulation and mental retardation [5]. Cerebellum is the most severely affected in CS, resulting in intentional tremors and ataxia [9]. The basal ganglia and thalamus are the next most severely affected structures, although there are wide variations among the affected children [2]. Cerebral white matter atrophy is more prominent, which may be the earliest neurological manifestation of CS. Rapin et al. [9] described patchy and segmental demyelination, characterizing the tigroid leukodystrophy [9]. Other uncommon CNS manifestations include stroke and subdural hemorrhage [8-10]. However, CS patients do not have any major brain malformations. There is a relative sparing of cerebral cortex and this may be the rationale for salvation of social skills until later stages [10]. Seizures occur in 23% of the children with CS [5]. Neuroimaging in CS reveals

cerebral and cerebellar atrophy, patchy/segmental demyelination and bilateral calcification in basal ganglia, subcortical white matter and dentate nucleus [2]. Calcifications may not be prominent until 3 years of age. Our index child had global developmental delay with microcephaly and hypertonia of lower limbs. However, the neuroimaging was normal.

The diagnosis of CS is based on the criteria laid down by Laugel et al. [4] “The major criteria include developmental delay, progressive growth failure and progressive microcephaly. The minor criteria include cutaneous photosensitivity, pigmentary retinopathy/cataract, progressive SNHL, enamel hypoplasia and enophthalmia.”

The peculiarity of our case is the pure neurological involvement without cardinal features of ophthalmological, dermatological and otorhinolaryngological system. Wilson et al. in their cohort of 102 CS patients described hearing loss in 84% of children by 10 years, cataract in 86% of children by 4 years, retinal dystrophy in 43% of children [5]. Kubota et al. [7] described hearing loss after 2 years of age, cataract in 64.5% and retinal dystrophy in 89.3% of CS. Natale et al. [11] described hearing loss in CS as universal but Nance and Berry [6] stated that hearing loss may not be manifested till teenage. Basal ganglia calcification and peripheral neuropathy have also been widely reported [5-7]. In a series of 8 cases of CS, Chikhaoui et al. [12] found that only one patient did not have ophthalmological manifestation, one patient did not have otorhinolaryngological abnormalities and all eight had dermatological manifestations. There was no patient who did not have both ophthalmological and auditory manifestations. To the best of our knowledge, this is the first CS case with a pure neurological phenotype without involvement of other systems. The relatively young age at diagnosis may be one of the plausible explanations behind the peculiar phenotype of our case. Additionally, our patient had normal neuroimaging which is quite rare, but has been described in 14 out of 85 patients by Wilson et al. [5] and 2/45 patients by Nance and Berry et al. [6].

Treatment for CS is mainly supportive as there are no specific treatment options that could halt or slow the progression of the disease. Annual eye and ear examinations, periodic neurological examination, physiotherapy for tone abnormalities, cochlear implants for hearing loss, sunscreen for photosensitivity, cataract surgery and tube feeding for malnutrition may be helpful. The mean age of death is around 12 years.

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