

COCKAYNE SYNDROME - A REVIEW

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Abstract: Cockayne syndrome is a rare disorder with a recessive autosomal inheritance. It is also known as Neill-Dingwall syndrome. Patients with this syndrome are characterized by short stature and an appearance of premature aging. Features of this disorder include a failure to gain weight and grow at the expected rate, abnormally small head size, photosensitivity and impaired development of the nervous system. Oral features present in this syndrome include delayed eruption of the primary teeth, congenitally absent of some permanent teeth, partial macrodontia, atrophy of the alveolar process and caries. It is described to be caused by two gene mutations, ERCC6 and ERCC8, causing two types of cockayne syndrome, CS-A, secondary to a ERCC8 mutation and CS-B with ERCC6 mutation. Mutantations of XPB, XPD and XPG genes are also associated with cockayne syndrome. This article provides information on the types of cockayne syndrome, causes, symptoms, clinical features and treatment. This article has been initiated to provide the readers with required information on the syndrome and to bring in an awareness about the presence and occurrence of cockayne syndrome with its possible characteristics. The aim of this review is to expand the knowledge of the clinical characteristics of children with cockayne syndrome.

Keywords: Recessive autosomal inheritance, Premature ageing, photosensitivity, CKN1 type, CSA type, CSB type, ERCC6 gene, ERCC8 gene, macrodontia, growth and development retardation.

INTRODUCTION

Cockayne syndrome is a rare disorder also known as Neill-Dingwall syndrome or Webber-Cockayne Syndrome. It is a rare autosomal recessive degenerative disease with abnormalities like cutaneous, ocular, neurological and somatic. It is characterized by short stature and an appearance of premature ageing. Failure to gain weight and grow at the expected rate, having an abnormally small head size, being photosensitive and impaired development of the nervous system are all a feature of this disorder. This syndrome occurs with a frequency of 1/1,00,000 in live births and the entity was first described in 1936 by Cockayne[1].

TYPES OF COCKAYNE SYNDROME

Clinically there are three different classes of CS and a subclass: A classical form (CS I) which includes the majority of patients, manifests during infancy, and death occurs in the first decades of life; a severe form (CS II) characterized by early onset which leads to death in infancy and severe progression of manifestations and a mild form (CS III), typified by late onset and slow progression of disease follows a more protracted course into adulthood. COFS is the recently identified CS subtype, is the most severe form, starting in utero or during the neonatal period with arthrogyriposis, microphthalmia, and congenital cataracts and has a rapid fatal outcome[3],[1],[2],[5]. Recently different level of severity groups have been described and renamed into severe, moderate, and mild CS. Mean age of death is 5, 16, and 30 years in these groups, respectively [8]. On account of clinical subgroups of decreasing severity, CS is classified into COFS, CS II, CS I, and CS III[2].

CAUSES

Cockayne syndrome can be caused by mutations of two genes, located on chromosomes 5 and 10q11, they are the Cockayne Syndrome Type I (CKN1) or Excision-Repair Cross-Complementing Group 8 (ERCC8) and the Excision-Repair Cross-Complementing Group 6 (ERCC6), respectively [9]. These mutations give rise to two variations of the syndrome, that is CS-A for the CKN1 and CS-B for the ERCC6. Mutation in ERCC6 accounts for 65% of cases[10], [11] whereas, mutation in ERCC8 accounts for 35% of cases[12]. Mutations in XPB (Xeroderma pigmentosum B) gene, XPD (Xeroderma pigmentosum D) gene and XPG (Xeroderma pigmentosum G) gene are also associated with cockayne syndrome [13]

CLINICAL FEATURES

Symptoms of all types of cockayne syndrome are similar. Neuro-developmental delay, failure to thrive, cutaneous photosensitivity, pigmentary retinopathy, neurosensory hearing loss, dental caries, and cachectic dwarfism are some of the clinical features of CS. If the first two clinical criteria and at least three of the other criteria mentioned above are seen in the patient then the diagnosis is very likely to be of CS. They also present delayed psychomotor skills and mental retardation, which lead to severe problems for talking and walking [14]. However, cases of normal intelligence have been reported [11]. The skin on the face, arms, and legs appears aged and wrinkled due to the loss of fat under the skin (subcutaneous adipose tissue). Children with this disorder have an increased amount of pigmentation in the skin and they tend to scar more easily. There are ophthalmologic diseases like pigmentary

retinopathy, degeneration of the retina, cataracts and decreased tearing. The patients commonly have hearing loss. Other frequent complications are liver and spleen enlargement, renal disease and hypertension [15], [16], [11].

Unusual physical features including microcephaly, an unusually thin nose, large misshapen ears, a “hollow” or sunken appearance to the eyes, poor eyelid closure, and/or prognathism are seen in children with Cockayne syndrome. Due to the abnormal placement of the teeth an unusual amount of dental decay might be present. Typically, affected individuals have large hands and feet, and unusually long arms and legs in proportion to the size of their body. Joints may also be abnormally large and remain in a fixed position (flexed), and the spine may be curved outward when viewed from the side (kyphosis). Other features of Cockayne Syndrome may include a decrease in the amount of sweating (hypohidrosis), lack of proper tearing in the eyes, and/or the premature greying of the hair. The pathophysiologic mechanisms behind the remaining clinical features are poorly understood[2].

Other anomalies

Oral manifestations or anomalies include Craniofacial anomalies and dysmorphism like microcephaly with retrognathia, high arched palate, atrophy of the alveolar process, condylar dysplasia, absence of few permanent teeth, and short roots. Nance and Berry mentioned about the orodental features like delayed deciduous tooth eruption, malocclusion, and absent/hypoplastic teeth but with no detailed analysis. Dental anomalies including dental caries are considered to be a minor diagnostic feature in this milestone paper together with photosensitivity, progressive retinitis pigmentosa, and deafness [17].

SYMPTOMS IN SPECIFIC

Symptoms related to the different classes or forms of cockayne syndrome are similar to one another but to be specific CS type I which is known to the classical form, is characterized by a normal appearing newborn whose symptoms might not be apparent until after the first year. Height and weight, as well as other indicators of size and growth are much within the 5th percentile. Central and peripheral functioning gets worse over time and might lead to severe disability. Obvious growth failure at birth along with little or no neurological development after birth are few characterized features in congenital CS type II cases. Serious vision impairments like cataracts and other structural abnormalities of the eye are usually present at birth. Early skeletal aberrations occur as well. CS type II also includes some patients who were previously diagnosed with cerebro-oculo-facial syndrome (COFS) and Pena-Shokeir type II syndrome due to the identification of a common gene defect in these patients. CS type III is the rare type of CS and it is characterized by essentially normal growth and mental development during the early years but is interrupted by the late onset of the typical symptoms of CS. The most rare form of CS is XP-CS and it includes the features of both the diseases. Early skin cancers and widespread freckling are typical features of xeroderma pigmentosa whereas short stature, mental retardation and sexual underdevelopment are consistent with CS.

TREATMENT

Although patients can be treated according to their specific symptoms, there is no permanent cure for this syndrome. The prognosis for patients with Cockayne syndrome is poor, as death typically occurs by when the individual reaches his twenties. Physical therapy and minor surgeries to the affected organs, like cataract removal are the type of treatment available for patients with CS. [19] Also wearing high-factor sunscreen and protective clothing is recommended as patients with Cockayne syndrome are very sensitive to UV radiation.[20] Optimal nutrition can also help. Genetic counseling for the parents is recommended, as the disorder has a 25% chance of being passed to any future children, and prenatal testing is also a possibility.[19] Another important aspect is prevention of recurrence of CS in other siblings. Identification of gene defects involved makes it possible to offer genetic counseling and antenatal diagnostic testing to the parents who already have one affected child[21].

CONCLUSION

The major characteristics of Cockayne Syndrome include dwarfism during late infancy, photosensitivity, and progeroid. Paediatric dentists play a significant role in managing the CS patient as craniofacial and oral anomalies and dental caries are common in the CS. The life expectancy for these individuals are relatively short. Early dental evaluation and parental counselling have the utmost significance. These individuals need a preventive dental regimens which must be individually designed and implemented because of reduced mandibular motion. Frequent visit to a dentist for examinations and emphasis on preventing dental disease must be stressed to the parents because of the difficulty in providing restorative care. Dietary counselling also plays an important role as overconsumption of any food that which may cause a dental issue may become difficult to treat. Appropriate and safe dental care for patients with CS can be rendered and medical consultation[18]. Hypomyelination, supratentorial white matter loss, cerebellar atrophy or hypoplasia, and bilateral putaminal calcifications are the most typical pattern recognised in classic and late-onset CS, often associated with cortical calcifications in early-onset types of the disease. These features can help differentiate CS from other leukodystrophies.

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