CASE REPORT

COCKAYNE SYNDROME: ROLE OF GENETIC COUNSELLING

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Cockayne's Syndrome (CS) is a rare autosomal recessive disorder characterized by deficiency in the transcription-couple DNA repair pathway caused by mutations in the genes ERCC6 in 65% of individuals and ERCC8 in 35% of individuals. Here we report a rare case of Cockayne's syndrome in a girl who presented with hallmark features specific to the syndrome. Dissemination of our knowledge about clinical manifestations encountered in Cockayne syndrome is instrumental not only for early evaluation and treatment to prolong life expectancy, but also to initiate early genetic counselling with parents concerning future pregnancies.

Keywords: Cockayne syndrome, photosensitivity, cataract

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INTRODUCTION

Cockayne's Syndrome (CS) is a rare autosomal recessive disorder, first described by Cockayne in 1936.[1] The incidence of CS in Western Europe has been recently evaluated as 2.7 per million. Patients with this syndrome present with failure to thrive, progressive cachectic dwarfism, photosensitivity with premature aging, neurological alterations, congenital cataract, retinal dystrophy, sensorineural deafness and congenital absence of some permanent teeth and caries.[2,3] The life expectancy of patients with Cockayne's syndrome is limited, but patients progress to adolescence and even early adulthood.[4]

Dissemination of knowledge of clinical manifestations encountered in CS patients play an instrumental role in the early evaluation as well as rendering appropriate care for patients. Thus, the present study aims at discussing a rare case of Cockayne syndrome highlighting the clinical and radiological features.

CASE REPORT

A 16-year old emaciated female patient having speech delay and psychomotor retardation reported to our hospital. History revealed no parental consanguinity and normal vaginal delivery at 41 weeks gestation.

Patient's mother had experienced feeding difficulties due to presence of cleft palate which was surgically corrected at the age of one year. On physical examination, patient was found to be of short stature and cachectic with height of 121 cm and weight of 32 kg.

Photosensitive dermatitis and dark pigmentations with reduced subcutaneous fat caused a prematurely aged appearance (Figure-1). Photosensitive dermatitis resulting in desquamation and scarring was also seen in the skin of neck and chest region (Figure-2). Fine sparse eyebrows, prominent beak nose and abnormal fold of pinna were also noticed.

Oral examination revealed scarred palate, multiple carious teeth and inflamed gingiva (Figure-3). Orthopantomograph revealed short roots and multiple missing teeth.

Lateral cephalogram showed no evidence of any intracranial calcification; however mid face hypoplasia with mandibular prognathism was noticed.

Ophthalmic evaluation revealed esotropia and corneal opacity in the right eye and iris coloboma in the left eye with bilateral early cataract. Partial syndactyly of the toes was noticed bilaterally (Figure-4). These clinical and radiological findings permitted us to consider a diagnosis of Cockayne syndrome.

Patient was given restorative care for carious teeth and gingivitis. A thorough home care program for adequate oral hygiene maintenance was designed and demonstrated to the parents.

Since vision improved with refraction for the left eye, no surgical intervention was planned. As the right eye was amblyopic, treatment would not be beneficial.

Patient was referred for physical therapy to maintain her ability to walk and to prevent joint contractures. Patient's parents were also educated about the use sunscreens and sunglasses for cutaneous photosensitivity. She was also advised to have specialized education for developmental delay.

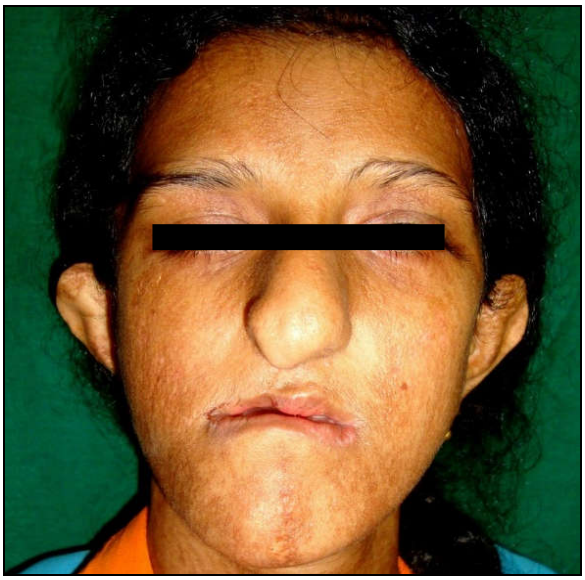

Figure-1: 16- year old patient showing characteristic senile appearance, fine sparse eyebrows, prominent beak nose and abnormal fold of pinna.

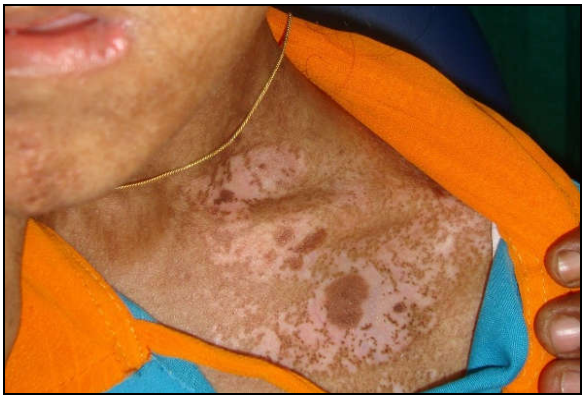

Figure-2: Photosensitive dermatitis resulting in desquamation and scarring seen in the skin of neck and chest region

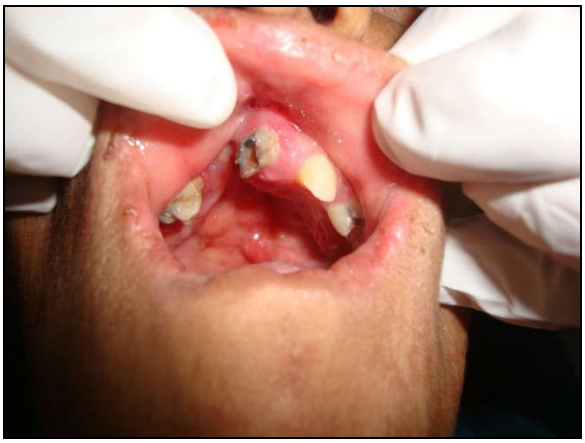

Figure-3: Intraoral view showing scarred palate, multiple carious teeth and inflamed gingiva

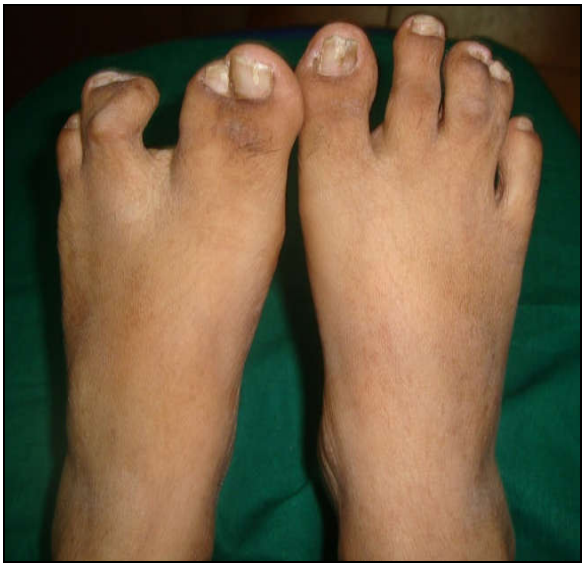

Figure-4: Partial syndactyly of the toes seen bilaterally.

Table-1: Phenotypic spectrum of cockayne syndrome

Features	Cs type I (Classic or moderate form)	Cs type II (Severe form)	Cs type III (Milder form)	XP-CS
Growth	-Normal prenatal growth. -Postnatal growth failure by age 2 years (height and weight <5th percentile)	-Growth failure at birth. -Little postnatal increase in height, weight, or head circumference;	Essentially normal growth and cognitive development or by late onset	-Short stature -No skeletal dysplasia
Neurologic	-Progressive microcephaly -Progressive behavioral and intellectual deterioration in all individuals; -Intracranial calcifications are seen in some individuals	-Little or no postnatal neurologic development. -Arthrogryposis or early postnatal contractures of the spine (kyphosis, scoliosis) and joints.		-Intellectual disability -Spasticity
Ophthalmic	Pigmentary retinopathy and/or cataracts	-Congenital cataracts -Structural defects of the eye (microphthalmos, microcornea, iris hypoplasia)		- No CNS dysmyelination and calcifications
Dermatologic	-Thinning of skin and hair -Photosensititvity	Photosensitivity		Facial freckling and early skin cancers typical of XP
Other features	-Sensorineural hearing loss -Severe dental caries	-Overlaps clinically with the cerebrooculofacioskeletal syndrome (COFS), which is also referred to as Pena-Shokeir syndrome type II.		
Prognosis	Death typically occurs in the first or second decade	Death by age seven years		

DISCUSSION

Edward A. Cockayne, a London paediatrician, first described this syndrome of "microcephalic cachectic dwarfism" in 1936 after examining two siblings age 6 and 7 years.[5] This syndrome occurred with a frequency of 1/100, 000 live births and can be caused by mutations of two genes, the CKN1 or ERCC8 (Excision-Repair Cross-Complementing Group 8), and the ERCC6 (Excision-Repair Cross Complementing, Group 6), located on chromosomes 5 and 10q11 respectively.[3]

The disease is characterized clinically by cachectic dwarfism, cutaneous photosensitivity, and loss of adipose tissue, mental retardation, skeletal and neurological abnormalities, and pigmentary degeneration of the retina.[4] Cockayne syndrome spans a phenotypic spectrum that includes CS type I, the "classic" or "moderate" form; CS type II, a more severe form with symptoms present at birth; CS type III, a milder form; Xeroderma pigmentosum-Cockayne syndrome (XP-CS).[6,7,12] (Table-1) Premature aging is associated with Cockayne's syndrome, and it may be differentiated from progeria by the absence of ocular anomalies and the cutaneous photosensitivity in the later.[8] The normal intelligence and presence of a relatively large skull with multiple wormian bones also tends to differentiate this disease from Cockayne's syndrome.[9] The hallmark of both Cockayne syndrome and xeroderma pigmentosum is a defect in DNA repair following ultraviolet irradiation, but the disorders differ in that unscheduled DNA synthesis after ultraviolet exposure is reduced in xeroderma pigmentosum and normal in Cockayne syndrome.[10] Both diseases are associated with an increased risk of sunburn and actinic skin atrophy but patients with Cockayne syndrome are not prone to development of cancer. Craniofacial abnormalities associated with the disease include a relatively small cranium with a thick calvarium.[4] Cerebral calcifications (particularly in basal ganglia) have been a frequent feature in cases with CS and have been related to decreased serum calcium. This differentiates CS from Progeria wherein premature arteriosclerosis, thin calvarium and open fontanelles are reported.[9] The rapidly progressing understanding of the specific genetic causes of Cockayne syndrome has enabled advancements in the diagnosis of the disease. Though initial diagnosis is made on the clinical presentations, it is confirmed by specific DNA repair assay on fibroblasts which show decreased recovery of RNA synthesis following exposure to ultraviolet light.[6] It can be diagnosed prenatally by examining amniotic cells cultured *in vitro*.[11] Carrier parents can be identified by gene tests enabling them to be better informed before they decide to have a child.[4]

These patients are treated by managing the manifestations which include: individualized educational programs for developmental delay, physical therapy to maintain ambulation and prevent joint contractures, medications for spasticity and tremor as needed, use of sunscreens and sunglasses for cutaneous photosensitivity and lens/retina protection respectively, treatment of hearing loss, cataracts, and other ophthalmologic complications as in the general population. Thorough homecare program for adequate oral hygiene maintenance and prevention of carries and yearly assessment for complications such as hypertension, renal or hepatic dysfunction, and declining vision and hearing is also needed.[7] Though comprehensive testing for Cockayne syndrome has developed greatly, better treatments have yet to be developed. Currently, the treatments continue to consist of the traditional methods to manage most symptoms and prevent others from arising or worsening. Thus specific attention to these clinical manifestations may not only contribute to diagnosis and help plan management but also to initiate early genetic counselling with parents concerning future pregnancies.

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