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Case Report

Cockayne syndrome: an uncommon clinical entity

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ABSTRACT

Cockayne syndrome is a rare autosomal recessive genetic disorder characterized by microcephaly, failure to thrive, and delayed development. It is associated with an abnormally small head size, stunted growth, and a high incidence of <1 in 250,000 live births. The clinical presentation of Cockayne syndrome varies widely, making diagnosis challenging, particularly in Southern India where limited data is available on its neurological manifestations. This case report describes a 23-year-old male patient presenting with neurological symptoms, highlighting the need for increased awareness and early detection of Cockayne syndrome in this region.

Keywords: Cockayne syndrome, Neurological symptoms, Microcepahly, Cockayne facies

INTRODUCTION

Cockayne syndrome is a rare autosomal recessive genetic disorder caused by genetic changes in the ERCC8 (CSA) or ERCC6 (CSB) genes.[1] It is characterized by microcephaly, failure to thrive, short stature, and delayed development and the incidence is <1 in 250,000 live births.[2] The syndrome is divided into four types based on severity and age of onset of symptoms. Type 1, also the "classical form", usually occurs at one year of age by stunting and neurological disorders, followed by a decline in vision and hearing. Type 2 (also known as cerebro-oculo-facio-skeletal syndrome) is a severe form and occurs at the earliest. Type 3 corresponds to a moderate form. Type 4 is xeroderma pigmentosa-Cockayne syndrome (XP-CS) combining the manifestations of both diseases.[1]

We present a case of Cockayne syndrome in a 23-year-old male and discuss the symptoms and diagnostic aspects of the case.

CASE REPORT

A 23-year-old male patient presented with tooth pain and loss of appetite, intermittent low-grade fever, and watery loose stools for 15 days.

On examination, the patient was conscious but non-communicable with global development delay and severe intellectual disability. The patient was thin built with severe muscle atrophy, was found to have microcephaly, contractures in lower extremities, scoliosis-lordosis, chest wall deformity, deformed ears, parrot beak nose, sunken eyes, large extremities with talipes deformities and persistent drooling saliva present throughout the examination. Anthropometry showed significantly low weight (17 kgs; <3rd percentile), length (126 cm; <3rd percentile) and occipitofrontal circumference (42 cm). Dental examination showed dental caries in the right upper molar and first premolar and neurological examination revealed developmental delay, gross muscle wasting, and reflexes could not be elicited, with muscle contractures seen in all limbs.

The patient had a history of three episodes of seizures since the age of 11, with no episodes in the past year. His developmental quotient was 12%. Natal history of the patient revealed an emergency LSCS, non-vigorous child who had to be resuscitated and microcephaly at birth.

Family history included a non-consanguineous marriage, with a terminated second pregnancy at 32-weeks gestational age due to similar features on a prenatal TIFFA

scan. His nutritional history revealed calorie deficit i.e. 947 kcal and protein intake was 16 gms.

Table 1 shows the initial hematological investigations done, which revealed low hemoglobin levels, prolonged aPTT and elevated INR.

Initial differential diagnosis considered were Hutchinson-Gilford progeria syndrome, Werner syndrome, Seckel syndrome, Laron syndrome. A clinical exome sequencing confirmed the diagnosis of Cockayne syndrome with a homozygous missense variation in the ERCC8 gene.

Management and outcome

The child was given supportive treatment, anti-seizure medications, occupational therapy and physiotherapy. The parents were counselled regarding genetic inheritance of the disease.

Table 1: Complete blood count and coagulation profile.

Parameters	Patient's values	Normal range
Hb (g/dl)	7.9	13.5-17.5
TWBC (/mm^3)	7400	4500-11000
Neutrophils (%)	62	54-62
Lymphocytes (%)	32	25-33
Eosinpohils (%)	02	1-3
Monocytes (%)	03	3-7
Basophils (%)	00	0-1
Prothrombin time (sec)	17.19	11-15
Bleeding time (min)	2.00	2-8
Clotting time (min)	4.00	8-15
aPTT (sec)	52.8	25-40
INR	1.78	≤1.1

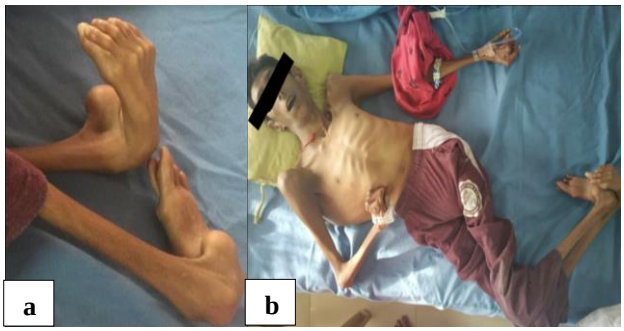

Figure 1: Note the characteristic cockayne facies, scolio-lardosis, chest wall deformity, talipes deformities.

DISCUSSION

Cockayne syndrome (CS) is a rare genetic disorder characterized by a range of clinical manifestations involving various systems. The diagnosis of CS is based on the criteria established by Laugel et al with major criteria including developmental delay, progressive growth failure, and progressive microcephaly. Minor criteria encompass cutaneous photosensitivity, pigmentary retinopathy/cataract, progressive sensorineural hearing loss (SNHL), enamel hypoplasia, and enophthalmia.[3]

The facial dysmorphism observed in CS patients includes wizened facies, sunken eyes, large ears, a thin pointed nose, and a small chin, often leading to the term "cachetic dwarfs".[4] SNHL is a cardinal manifestation of the disease. Ophthalmological complications commonly involve cataracts, corneal opacification, and pigmentary retinopathy.[5,6] Dermatologically, CS is characterized by photosensitivity, wrinkled and aged skin.[7] Cataracts, retinal degeneration and optic atrophy are also frequent, although not present in mildly affected cases.[8,9]

Neurologically, CS presents significant morbidity. Severe microcephaly, typically manifesting after infancy and present in all individuals by the age of two, is a prominent feature.[7] Delayed milestones contribute to motor dysfunction, ambulation difficulties, and mental retardation.[4] Cerebellar involvement leads to intentional tremors and ataxia, while the basal ganglia and thalamus are also affected. Cerebral white matter atrophy and patchy/segmental demyelination are commonly observed. Seizures occur in approximately 23% of CS children. Neuroimaging reveals cerebral and cerebellar atrophy, patchy/segmental demyelination, and bilateral calcification in the basal ganglia, subcortical white matter, and dentate nucleus.[2,4,10,11]

Although CS affects multiple systems, the presented case demonstrates major neurological involvement with minimal or no involvement of other systems. This unique presentation highlights the importance of recognizing the diverse clinical spectrum of CS and the need for increased awareness and early detection.

CONCLUSION

Cockayne syndrome is a rare genetic disorder characterized by microcephaly, failure to thrive, and delayed development. It affects multiple systems and has various clinical manifestations. Early diagnosis and appropriate genetic counselling are essential. This case highlights the importance of recognizing the symptoms and conducting genetic testing for an accurate diagnosis.

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