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Case Report

Cockayne syndrome, xeroderma pigmentosa: a rare case report

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ABSTRACT

Cockayne syndrome is a rare autosomal recessive disorder characterized by premature ageing (progeria), facial anomalies, cachectic dwarfism, mental retardation, cutaneous photosensitivity, and retinopathy, loss of adipose tissue and muscle, and neurological abnormality which are associated with the changes in the brain parenchyma. The findings of computed tomography scan and especially magnetic resonance imaging of the brain support the clinical diagnosis of CS. There is no permanent cure of this condition and death usually occurs in the second or third decade due to functional disability and multiple infections.

Keywords: Brain, Cockayne syndrome, Magnetic resonance imaging, Progeria

INTRODUCTION

Cockayne syndrome (CS) is a rare autosomal recessive disorder occurs in about 1 case per 2.77 million births.[1] It was first described by Cockayne in 1936, and till now, around 150 cases have been reported in literature.[2] CS is associated with mutations in the gene CS type A (CSA)/excision-repair cross-complementing protein (ERCC) 8 or CS type B (CSB)/ERCC6 which provide instructions for repairing damaged DNA.[3] Clinically, three types of CS have been described in literature as classical, milder, and severe form depending on the time of presentation and severity of the clinical symptoms and final outcome.[4] The classical features of CS are progressive loss of subcutaneous fat and muscle, mental retardation, premature ageing, dwarfism, facial abnormalities, microcephaly, retinopathy, protruding neck, hearing loss, dental changes, large extremities, joints contracture, photosensitivity, dry skin, and hair.[5,6] Intracranial calcification and brain atrophy are seen in most of the individuals. Early diagnosis is very important for patient management and proper parental genetic counselling.

Xeroderma pigmentosum-Cockayne syndrome complex (XP-CS) is a very rare neurodegenerative disorder that combines clinical features of xeroderma pigmentosum (XP) with those of Cockayne syndrome (CS).

CASE REPORT

A 8 year old girl presented with history of skin hyperpigmentation over malar and nasal area of face since the age of 6 months and swaying while walking on either side since age of 2 years. She was born to a secondary consanguineously married couple, with normal birth history and global developmental delay. There was also significant family history of similar complaints in younger sibling (2 of 5 siblings were affected).

On examination, she was stunted (with height 111 cm, <3rd centile for age), wasted (with weight 16kg, <3rd centile for age) and had microcephaly (head circumference of 47 cm, <-2 SD for age). Spasticity was present in all four limbs with left sided spasticity more than right side. Exaggerated reflexes with extensor type of plantar reflex were present. Signs of cerebellar

dysfunction were present with spastic type of gait as shown in (Figure 4).

On investigation brainstem evoked response audiometry (BERA) showed right ear severe hearing loss. Fundus examination was normal. Magnetic resonance imaging (MRI) showed demyelination of anterior temporal lobe white matte, U fibres along bilateral frontal white matter, peri trigonal white matter and corona radiate. Mild degree of cerebral and cerebellar atrophy. On the basis of history, clinical examination and investigations probable diagnosis of xeroderma pigmentosum-Cockayne syndrome complex was made. Further cytogenetic evaluation for confirmation of diagnosis is planned.

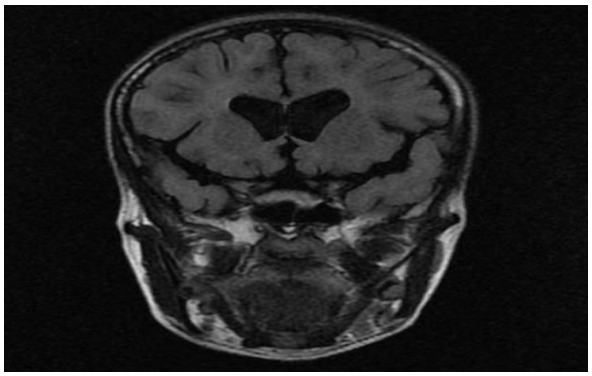

Figure 1: Abnormal symmetrical T2 hyperintenisties seen involving anterior temporal lobe white matter, U fibers along the bilateral frontal white matter, peri trigonal white matter and corona radiate.

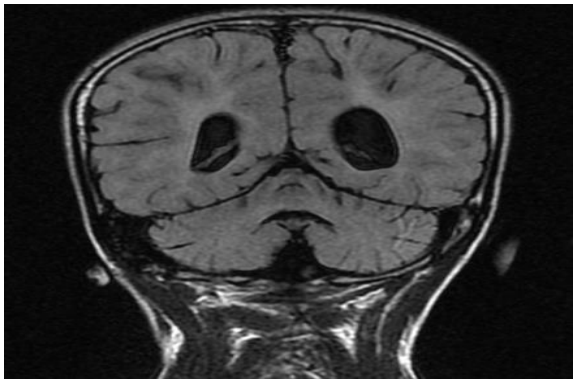

Figure 2: Hypo/dysmyelination involving anterior temporal lobe white matter, U fibers along the bilateral frontal white matter, peri trigonal white matter and corona radiate.

DISCUSSION

CS is an autosomal recessive disorder with incidence around 1 case per 2.77 million births.[1] The basic pathology is deficient DNA repair mechanism due to mutation in gene CSA/ERCC8 and CSB/ERCC6 located on the chromosomes 5 and 10, respectively.[2] Despite these, principle genes sensitivity of the patient fibroblaststo ultraviolet C irradiation has been considered the diagnostic test of choice.[7] Important feature in CS is that in spite of deficient DNA repair, patients do not develop cancer. The CS consists of progressive neurodegeneration, mental retardation, progeria, ataxia, dwarfism, facial dysmorphism, microcephaly, abnormal photosensitivity, hearing loss, and joints contracture.[5,8]

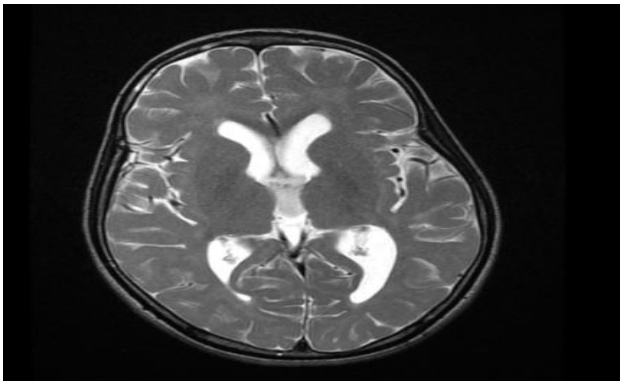

Figure 3: Mild degree cerebral and cerbellar atrophy.

Figure 4: Eight year old girl with clinical features of Cockayne syndrome-xeroderma pigmentosa.

CS is a rare entity and around 150 cases have been reported in literature up till now.[2] Male to female ratio is 4:1. This syndrome does not get over until 4-5 years of age where growth and development almost appear normal and after that manifestation of progressive neurodegenerative changes become evident. Most of the patients live up to the 2nd decade and finally die due to severe respiratory and other infections.[6]

Three types of CS described in the literature. Type I is the classical form and includes majority of the patients and present with normal fetal growth and onset of abnormality in the first 2 years of life. Peripheral and

central nervous systems progressively degenerate until death in the first or second decade of life due to severe neurological disorders. Cortical atrophy is not severe in this type. Type II is severe form present since birth. Neurological development is very poor after birth and deathusually occurs around the age of seven.[4] This is also called as cerebro-oculo-facio-skeletal syndrome.[4] Brain shows more severe damage including reduced myelination of white matter and more widespread calcification in the basal ganglia and cortex.[9]

Type III is the milder form characterized by the late onset slow progression and these patients live up to adulthood.[4] Failure to thrive and neurological disorder are criteria for the diagnosis while photosensitivity, ophthalmic changes, sensorineural deafness, and dental disorder are other very common manifestation.[10] The neurologic changes are neuronal and myelin loss with calcium and iron deposition in the small vessels of the basal ganglia, cerebrum, and cerebellum. This neurodegeneration commonly presents as progressive mental retardation and ataxic gait. The other classical features are retinitis pigmentosa and photosensitive dermatosis.

The clinical findings in our patient permitted us to establish a diagnosis of Cockayne's syndrome-xeroderma pigmentosa (CS-XP) a rare variant as shown in (Figure 4). Correlating the syndrome with the CBS gene mutation is not possible, however, we hypothesize that the mutation gives rise to the protein responsible for coding the gene due to its absence resulting in a much more abnormal phenotype. In current case, patient presented with xeroderma pigmentosa, progressive mental deterioration, sensoneuronal deafness with ataxic gait.

Neuroimaging including CT and MRI (T2 weighted and FLAIR) is the modality of choice for evaluation of brain. MRI of the brain shows atrophy of the brain in supratentorial and infratentorial aspect along with hyperintense signal of the cerebral white matter on T2-weighted and FLAIR images representing hypomyelination/demyelination. Early age basal ganglia calcification also prompts toward the syndrome along with cerebral and cerebellum calcification.[10] MRI results are compatible with diffuse cerebral white matter demyelination showing abnormal signal change.

The MRI of our patient also showed abnormal symmetrical T2 hyperintenisties seen involving anterior temporal lobe white matter, U fibers along the bilateral frontal white matter, peri trigonal white matter and corona radiate as shown in (Figure 1). Hypo/dysmyelination involving anterior temporal lobe white matter, U fibers along the bilateral frontal white matter, peri trigonal white matter and corona radiate as shown in (Figure 2). Mild degree cerebral and cerbellar atrophy were also present as shown in (Figure 3).

In the appropriate clinical setting, MRI features of brain atrophy, white matter changes and bilateral cerebral are sufficient to support to our diagnosis. No permanent cure of this disorder and patient treated according to their symptomatology. Genetic counselling of the parents is advised as the disorder has about 25% chance of penetration into any future offspring.

CONCLUSION

Cockayne's syndrome is a rare, devastating autosomal recessive disease resembling progeria. Craniofacial and oral anomalies and dental caries are common in the syndrome. Although life expectancy is relatively short for these individuals, the pediatric dentist plays a significant role in managing the Cockayne's syndrome patient. Early dental evaluation and parental counselling have the utmost significance. Preventive dental regimens must be individually designed and implemented because of reduced mandibular motion. Dietary counselling is extremely important because of a propensity for dental caries and low weight. Frequent examinations and emphasis on preventing dental disease must be stressed to the parents because of the difficulty in providing restorative care. Appropriate and safe dental care for patients with Cockayne's syndrome can be rendered after medical consultation.

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