Cockayne syndrome – A case report

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ABSTRACT

Cockayne syndrome (CS) is a rare multisystem disorder, with autosomal recessive inheritance. It belongs to the family of nucleotide excision repair diseases with clinical features of failure to thrive, neurodevelopmental delay, cutaneous photosensitivity, pigmentary retinopathy, neurosensory hearing loss, dental caries, premature ageing (progeria), and cachectic dwarfism with associated changes in the brain parenchyma. The imaging findings of the brain along with clinical features are helpful in the diagnosis of CS. There is no permanent treatment option for this condition and death usually occurs due to functional disability/infection by the end of the 3rd decade. We would like to highlight the imaging profile (computed tomography and magnetic resonance imaging findings) of this rare syndrome.

Key words: *Brain, cockayne syndrome, leukodystrophy, radiology*

Cockayne syndrome (CS) is a rare autosomal recessive, multisystem disorder, belongs to the family of nucleotide excision repair diseases along with xeroderma pigmentosum. CS is caused by 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. Clinical features include failure to thrive, neurodevelopmental delay, cutaneous photosensitivity, pigmentary retinopathy, neurosensory hearing loss, dental caries, and cachectic dwarfism which are associated with the changes in the brain parenchyma [1-4]. The diagnosis is made by clinical features along with imaging features. CS includes a wide spectrum of clinical severity, which has been subdivided into four overlapping clinical subgroups of decreasing severity. Intracranial calcification and brain atrophy are seen in most of the individuals. Progression of syndrome leads to functional disability with multiple infections leads to death within in the 3rd decade of life [5,6]. Early diagnosis is very important for patient management and parental genetic counseling. We present a case of CS with its radiological profile which is helpful along with classical clinical profile to make the diagnosis of this rare syndrome [7-11].

CASE REPORT

A 7-year-old female presented with difficulty to stand from sitting position, difficulty in walking, photosensitive rash on face for 7 months of age (which increases on exposure to sun), stunted growth, and not able to read and write.

Anthropometry measurements include: Weight - 10 kg (−6 SD), height - 88 cm (−5 SD), head circumference - 42 cm (−6 SD). On examination, she had short stature, microcephaly, mental retardation, triangular facies, facial rash (Fig. 1), low set ears, dental caries, mild hypotonia, and generalized proximal muscle weakness (Gower's sign-positive). Ophthalmic examination showed photophobia and hereditary retinal degeneration with pallor of optic disc; no evidence of cataract or nystagmus; pupillary reactions were normal. Otorhinolaryngology examination was normal except for mild sensorineural hearing loss. Superficial and deep reflexes were reduced; cardiovascular, respiratory, and abdominal examination was within normal limits; routine blood biochemistry and serum creatine phosphokinase levels (248 U/L) were normal. Then, the patient was subjected to computed tomography (CT) followed by magnetic resonance imaging (MRI) brain study. CT brain showed bilateral putaminal calcification and few cortical calcifications (Fig. 2). The MRI of the brain, without a contrast study, showed generalized mild cerebral and cerebellar atrophies with widened sulci and an enlarged fourth ventricle, calcifications of the bilateral basal ganglia which are the classical features of CS (Figs. 3-5). MR spectroscopy showed normal NAA (N-acetylaspartate), choline, and creatinine peaks with decreased choline/creatine ratio and mildly increased lactate in some areas of white matter. The imaging features along with classical clinical features, we arrived the diagnosis of the CS. The parents of the patient have been explained the prognosis of the disorder and advised for the general care of patient according to the symptoms.

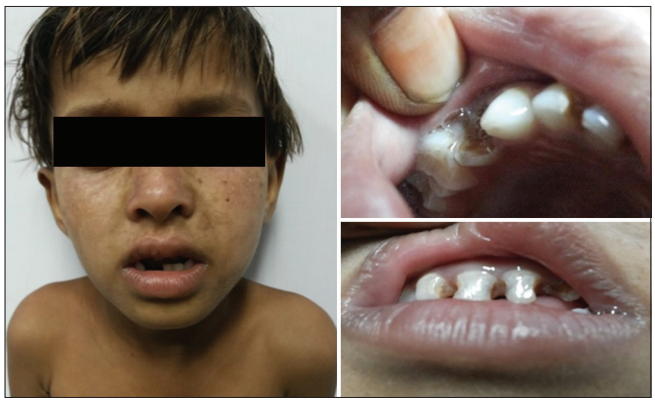

Figure 1: Clinical photograph of 7 year old female shows, traingular face with rash, low set ears and dental caries

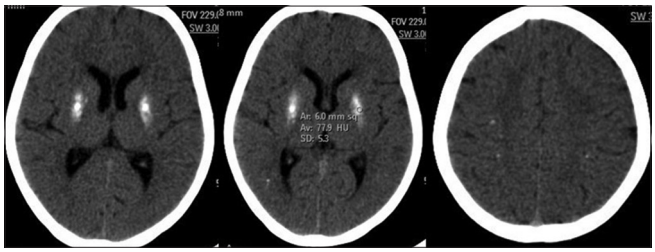

Figure 2: Axial non contrast CT images of brain at the level of basal ganglia confirms calcifications in bilateral lentiform nuclei and few subcortical calcification in bilateral parietal lobes.

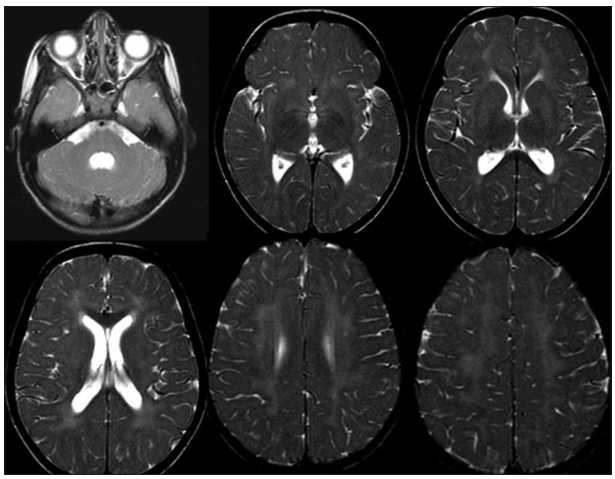

Figure 3: T2WI axial images of MRI brain shows mild diffuse cerebral and cerebellar atrophy with prominence of ventricular system, white matter hyperintensities and hypointensity in bilateral lentiform nuclei (indicates calcification)

DISCUSSION

The CS is an autosomal recessive, multisystem disorder with prevalence of 2 to 3 per million and male-to-female ratio of 3:1; classical clinical features include abnormal photosensitivity, retinitis pigmentosa, cachectic dwarfism, microcephaly, neurosensory deafness, and dental caries with progressive encephalopathy [1-4,12]. This syndrome often undetected in infancy, during which the growth and development are normal. The progressive degeneration is manifested by the 2nd or the 3rd year of life. All classical features were noted in our patient except of proximal muscle weakness, which was also reported in literature with unknown etiology; it may be due to cerebellar involvement.

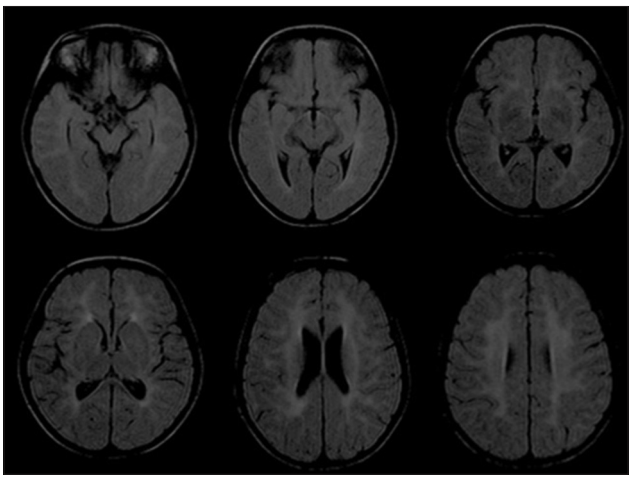

Figure 4: FLAIR axial images of MRI brain shows mild diffuse cerebral and cerebellar atrophy with prominence of ventricular system and diffuse white matter hyperintensities in periventricular and subcortical regions

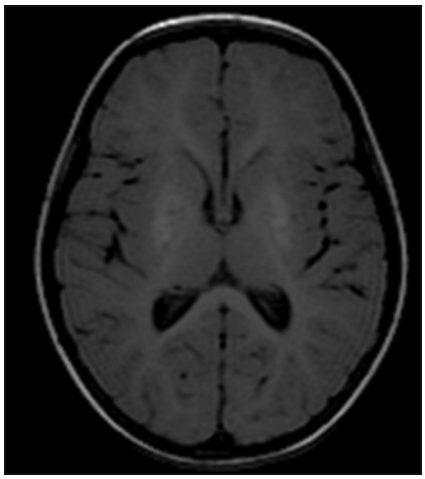

Figure 5: Axial T1WI brain MRI shows T1 hyperintensities in bilateral lentiform nuclei indicates calcification

It encompasses a wide spectrum of clinical severity, which has been divided into four overlapping clinical subgroups of decreasing severity: Cerebro-oculo-facial-skeletal syndrome (COFS), CS II, CS I, and CS III. COFS is the most severe form, starting *in utero* or during the neonatal period with arthrogryposis, microphthalmia, and congenital cataracts and has a rapid fatal outcome. CS Type II begins and leads to death in infancy. CS Type I (the classic form) manifests during infancy, and death occurs in the 1st decades of life. CS Type III shows milder signs and follows a more protracted course into adulthood [5-8].

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; mutations in these genes lead to a lack of recovery of RNA synthesis in cultured skin fibroblasts after ultraviolet irradiation, a key feature used as the major cellular

diagnostic test for CS; this may well explain the cutaneous photosensitivity of patients with CS, but the pathophysiologic mechanisms behind the remaining clinical features are poorly understood. The neuropathologic changes include neuronal and myelin loss with deposits of calcium and iron in the vessels in the cerebellum, the basal ganglia, and the cerebrum [1,2]. The previously reported radiological findings of the CS include atrophy of the brain stem, cerebellum and the cerebrum, high signal intensity of the cerebral white matter on T2-weighted images and fluid-attenuated inversion recovery, calcifications of the dentate nucleus of the cerebellum, and the basal ganglia; subcortical calcification and calcified leptomeningeal vessels also described in literature [3]. Its diagnosis is based on the clinical diagnostic criteria, and it may be supported by the demonstration of the intracranial calcifications and MRI findings [5-10]. The calcification of the basal ganglia and the subcortical white matter may be detected on CT as early as 3 years of age [3]. MRI is a sensitive tool which can demonstrate the white matter hypomyelination [6].

The MRI in our patient showed diffuse white matter atrophy with demyelination (Figs. 3-5). Along with clinical and imaging features, diagnosis of CS was made, and parents were counseled regarding prognosis, natural course of disease, life expectancy, and 25% possibility of inheritance to offsprings; genetic analysis was not advised, because of classical radiological and clinical profile. From our observation, it was not possible to differentiate the CS from the other white matter diseases in the absence of the putaminal and few punctate subcortical calcifications. In the appropriate clinical settings, the MRI features such as hypomyelination, supratentorial white matter loss, cerebellar atrophy or hypoplasia, and bilateral basal ganglia calcifications are an important adjunct for supporting the diagnosis of the CS.

There is no definitive treatment available for CS and our patient was treated symptomatically; expected life expectancy may be up to the 3rd decade of life [5,12] which could not be prolonged by any type of treatment.

CONCLUSION

Hypomyelination, supratentorial white matter loss, cerebellar atrophy or hypoplasia, and bilateral basal ganglia calcifications are the most typical features in CS, which are often associated with the cortical calcifications in the early-onset types of the disease. These features can help in differentiating the CS from other leukodystrophies.

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