Cockayne Syndrome. Report of three cases in a South African family of Indian origin.

Y Y, B PLA, P V

Citation

Y Y, B PLA, P V. *Cockayne Syndrome. Report of three cases in a South African family of Indian origin.*. The Internet Journal of Neurology. 2009 Volume 12 Number 2.

Abstract

Cockayne Syndrome (CS) is a multisystem photosensitive genetic disorder due to a defect in DNA repair. The hallmarks of Cockayne syndrome are postnatal growth failure and progressive neurological dysfunction. We describe three patients; A 23 year old female with psychomotor and growth retardation, difficulty with ambulation and impaired hearing and her 2 cousins; a 17 year old male and his 13 year old brother both referred with similar problems. The mothers of the patients are sisters and their fathers are brothers.

INTRODUCTION

Cockayne Syndrome (CS) is a multisystem photosensitive genetic disorder due to a defect in DNA repair. The hallmarks of Cockayne syndrome are postnatal growth failure and progressive neurological dysfunction. We describe three patients; A 23 year old female with psychomotor and growth retardation, difficulty with ambulation and impaired hearing and her 2 cousins; a 17 year old male and his 13 year old brother both referred with similar problems. The mothers of the patients are sisters and their fathers are brothers.

CASE A

A 23-year-old Asian female presented with short stature, deafness, mental retardation and difficulty with ambulation. She was born following an uncomplicated pregnancy and delivery. Her motor milestones were delayed. She was able to function normally as an 8 year old and attended mainstream school. After the age of 9 she showed gradual cognitive deterioration and eventually became dependant for most of her activities of daily living. She was unable to communicate basic needs, experienced increased skin sensitivity to sunlight and had progressive imbalance. She had poor appetite and stopped growing after the age of 8. Both parents were normal with no other family history of a similar problem in previous generations.

Her weight and height were below the 5th percentile for age. She had a progeroid appearance with a beaked nose, reduced subcutaneous fat and large sunken eyes. Skin examination revealed an erythematous rash in a butterfly distribution on her face. She had bilateral conjunctival injections with corneal ulcerations.(Fig. 1)

Central nervous system examination revealed severe mental retardation and she was only able to communicate a few words. Her speech was dysarthric. There was bilateral sensori-neural deafness. Her power and tone were normal. Tendon reflexes were symmetrically brisk and the plantar responses were flexor. Sensation was normal. Co-ordination was normal in the upper limbs and ataxic in the lower limbs. Her gait was broad–based and ataxic.

The following blood tests were normal: Full blood count, urea and electrolytes, liver function tests, creatinine kinase, lipid profile, glucose, follicular stimulating hormone, luetenising hormone, thyroid function test, oestradiol, growth hormone, Vitamin B12, folate and urine and serum osmolality. The prolactin level was elevated to 653,9uIU/ml (72-511). MRI scans of her brain revealed severe generalized cerebral and cerebellar atrophy with symmetrical periventricular T2 white matter hyperintensities. Bilateral basal ganglia calcification was present. MRI spine revealed generalized cord atrophy.

CASE B

A 17-year-old male presented with short stature, deafness, poor balance and skin sensitivity to sunlight. Pregnancy and birth were normal and he had normal development until age 6. He subsequently had growth failure with learning difficulty and behavioral problems. He was able to feed,

bathe and dress himself as well as communicate his basic needs. He could not read or write. He suffered frequent falls due to imbalance and would drag the lower limbs when walking.

Examination revealed a short and underweight for age teenager with a high-pitched voice of nasal character. He exhibited poor co-operation during mental state examination but was able to communicate in full sentences and occasionally answer appropriately. Apart from bilateral sensori-neural hearing impairment, the rest of the cranial nerve examination, including funduscopic examination, was normal. He had mild scoliosis. The lower limbs were spastic with normal power. Reflexes were symmetrically brisker in the lower limbs and the plantar responses were flexor. Sensation to pinprick was normal. Joint position sense could not be reliably tested. Co-ordination was normal.

Serological investigations were normal except for an elevated prolactin level of 532uIU/ml (86-390). MRI scan of the brain showed generalized cerebral and cerebellar atrophy.

CASE C

The 13-year-old brother of Case B presented with hyperactivity, delayed motor milestones, mental retardation, hearing impairment, skin sensitivity to sunlight and an abnormal gait.

His sister (21) is unaffected. He was on Ritalin for his hyperactivity.

Examination revealed him to be uncooperative and hyperactive. He obeyed simple commands and spoke sentences with a dysarthric speech. He had no cranial nerve palsies and his power was normal. He was spastic and ataxic in both lower limbs.

No further investigations were performed.

Figure 1

Figure 1. Case A. Bilateral conjunctival injections with inferior corneal ulcerations

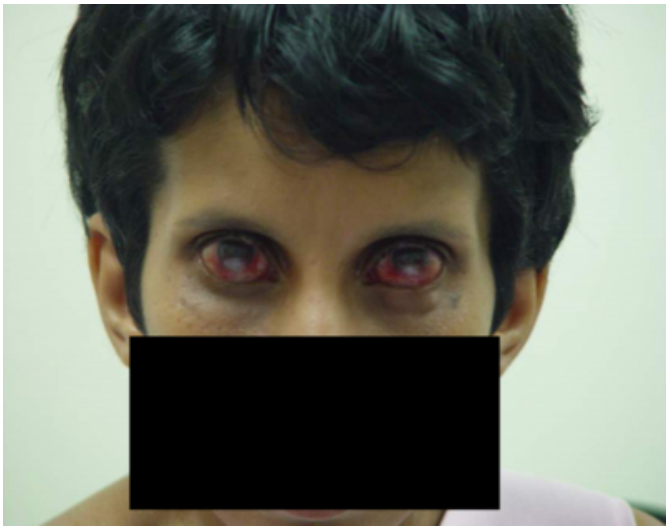


Figure 2

Figure 2. Case B showing small stature

Figure 3

Figure 3 MRI brain (Case A) Bilateral symmetrical T2 - weighted white matter hyperintensities.

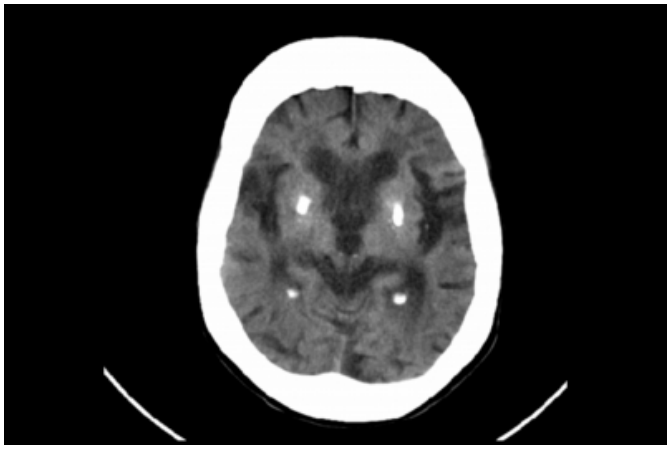


Figure 4

Figure 4 CT scan (CaseA) Bilateral basal ganglia calcification and generalized cerebral atrophy.

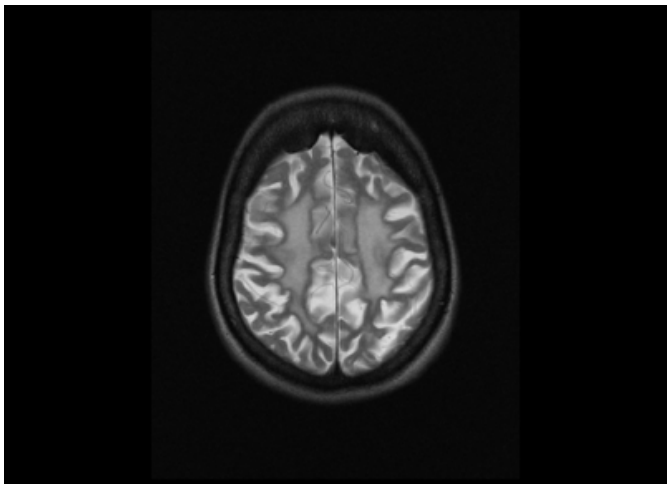
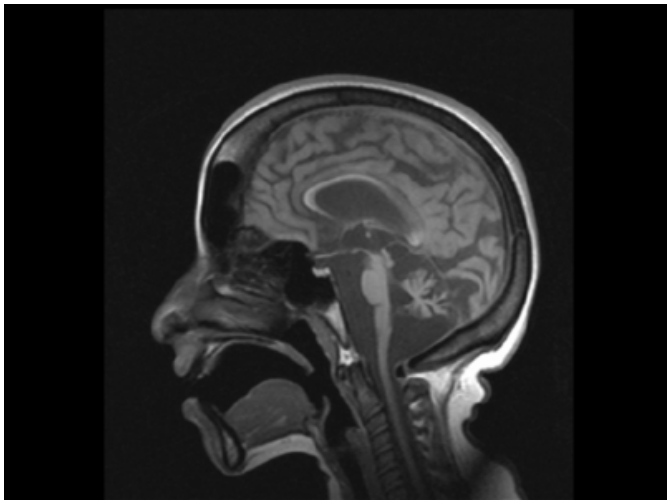


Figure 5

Figure 5 T1- weighted MRI image (Case A). Marked cerebral, cerebellar and brainstem atrophy



DISCUSSION

Cockayne syndrome, first described by E.A. Cockayne in 1936 [1], is a rare autosomal recessive disorder that results in postnatal growth failure and progressive neurological dysfunction.

Two complementation groups (CS-A and CS-B) have been identified and the majority of cases have been assigned to the CS-B group.[2] The genes responsible for CSA and CSB are ERCC8 and ERCC6 respectively.[3;4] The proteins encoded by these genes play important roles in a process of DNA repair viz. transcription-coupled nucleotide excision repair. This abnormal DNA repair has been documented in fibroblasts of CS patients and is manifest by increased sensitivity of CS fibroblasts to ultraviolet (UV) radiation and decreased recovery of RNA synthesis after UV exposure. [5]. The clinical spectrum of CS includes CS1 or “classic CS”, a severer form designated CS2 and two less frequent variants. These include, “Mild CS” where patients have relatively normal intelligence and growth with other genetic and clinical features of CS [1]. , and secondly, an overlap of CS and Xeroderma pigmentosa (XP). Patients in this category share features of both diseases. CS patients unlike XP are not at greater risk for cancers. [2, 9]

CS1 is less severe than CS2. Clinical features of CS in its “classic” form include postnatal growth failure with weight and height usually below the fifth percentile. Almost all patients beyond 2 years of age are microcephalic.

Neurological manifestations occur in all patients with delayed psychomotor development and mental retardation

being the most common. Sensori-neural hearing loss has been reported in more than 50% of cases. [1]

The commonest ophthalmologic findings are pigmentary retinopathy of the 'salt and pepper' type, cataracts and optic atrophy. Corneal ulcerations have been reported as a rare finding. [1] Seizures have been reported in 10% of cases. [6] Other neurological manifestations include spasticity, abnormal gait, ataxia, incontinence, tremor, abnormal or absent speech, weak cry or poor feeding in infancy, and behavioral abnormalities. [1]

Dermatological findings include increased skin sensitivity to sunlight in over 75% of patients, dry skin with thin dry hair, anhidrosis and a malar rash. Subcutaneous lipoatrophy together with the above dermatological features result in the progeroid appearance. [1] A thin slender nose with sunken eyes are common features giving patients with CS a characteristic somatic appearance.[7] Dental caries is very common. Skeletal abnormalities include disproportionately long limbs, large hands and feet, and flexion joint contractures.[8] Cryptorchidism , renal dysfunction and rarely hepatomegaly, splenomegaly, osteoporosis, emphysema have been reported. [1]

CS 2 patients have an earlier and more severe presentation with low birth weight, poor postnatal increase in weight, height and head circumference, and little if any neurological development. [1] Congenital and structural eye anomalies are considered predictors of early onset and severe disease.

Routine laboratory investigations are normal. Radiological characteristics of CS include a thickened calvarium, cerebral and cerebellar atrophy, ventriculomegaly, calcification of the basal ganglia and T2 white matter hyperintensities on magnetic resonance imaging. Electroneurography commonly shows slowing of nerve conduction and demyelination has been confirmed on nerve biopsies. [1; 8]Some of the more specific tests that are available on a research basis only include RNA synthesis inhibition assay and complementation testing.

The prognosis of CS is poor. Death occurs by age 8 in CS2 and by the second or third decade in CS1. The commonest cause of death amongst reported cases of CS is pneumonia. [1]

Our patients display characteristic phenotypic features of CS1. Our centre does not have the genetic tests necessary for confirmation. The pattern of the affected individuals as well as the relationships between the parents, support an autosomal recessive pattern of inheritance. Ancillary laboratory tests excluded other causes and the MRI and nerve conduction tests show features in keeping with CS.

To the best of our knowledge this is the first description of CS in South Africa.

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Author Information

Yacoob Y
Department of Neurology, Inkosi Albert Luthuli Central Hospital

Bill PLA
Department of Neurology, Inkosi Albert Luthuli Central Hospital

Patel V
Department of Neurology, Inkosi Albert Luthuli Central Hospital