Cockayne syndrome in 2 siblings

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ABSTRACT

Cockayne syndrome is a rare autosomal recessive condition characterized by growth failure and multisystem progressive degeneration. We report and describe this syndrome in a Jordanian brother and sister with Cockayne syndrome with first cousin parents. Clinical features included short stature, cachectic senile look, neurological deterioration, photosensitivity, mental retardation, hearing impairment and carious teeth. The phenotype is compatible with a mild variant of type I Cockayne syndrome. They showed an exaggerated response to growth hormone provocation test, with slightly elevated basal insulin-like growth factor 1 levels. The radiological findings of thinning of ribs and slender femora with narrow medullary canals have not previously been reported in this syndrome. We discuss the implications of these findings.

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Cockayne syndrome (CS) is a rare autosomal recessive condition characterized by growth failure and multisystem progressive degeneration. Clinical features include short stature, cachectic senile look, neurological deterioration, photosensitivity, retinopathy, cataract, mental retardation, hearing impairment, carious teeth and joint contractures.[1] Cockayne syndrome spans a spectrum that includes 4 subtypes depending on the clinical profile. Cockayne syndrome type 1 is the classic form with onset around 2 years of age, progressive developmental and neurological deterioration and a median survival to the age of 12 years. Longer survival seems to be correlated with the absence of cataract in the patient.[1] Cockayne syndrome type 2 is the more severe congenital form that manifests at birth with early death. Cockayne type 3 is the mildest form, with a later onset, and survival to adulthood.[1,2] The fourth type combines the features of CS and xeroderma pigmentosa (CS-XP). A transcription and DNA repair deficient syndrome, with a complex genotype-phenotype correlation describes CS.[3] The objective of the study is to report a family with a mild form of CS type 1 from Jordan. The 2 affected siblings in this family showed an exaggerated response to growth hormone provocation test, and the specific radiological findings of thinning of ribs and slender femora with narrow medullary canals. We discuss the clinical diagnostic criteria found in these patients in comparison to the literature.

Case Reports. ***Patient One.*** A male patient aged 17-years (proband) presented to the genetics clinic of the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman with the main complaints of short stature and tremor. He was born to first cousin parents of Palestinian origin after a normal delivery and birth weight of 3 kgs. He has one younger affected sister, patient 2, 2 younger unaffected sibs and 3 elder unaffected paternal half brothers. Feeding difficulties with recurrent vomiting and poor weight

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gain developed during the neonatal period, followed by gain in weight during infancy. Developmental milestones were uneventful. He had a history of removal of his right testicle, with no medical report to explain the indication. Parents reported that around the age of 6-8 years, his growth markedly slowed down, his performance in school started to deteriorate and he dropped school 2 years later. At that same time he started to have difficulty in performing delicate tasks due to trembling hands, and his gait was noticed to be unsteady, with no falling tendency. At presentation his height was 121 cm (z-score - 6.59), weight 23 kg (z-score - 10.68), head circumference 50 cm and arm span 121 cm. His features included triangular face, enophthalmos, prominent nose, micrognathia, high arched palate and dental caries. Butterfly malar photosensitive erythematous rash was apparent at the time of his initial presentation during the summer months with marked amelioration during winter. Neurological examination revealed the presence of a wide based gait with inability to perform tandem gait, dysmetria and dysdiadochokinesia, nystagmus and intentional tremors. He had well-developed secondary sexual characteristics, external genitalia and pubic hair being at Tanner stage 4. He showed a markedly exaggerated response to growth hormone (GH) provocation test with the GH level reaching a maximum of 140.74 ng/ml during the insulin hypoglycemia test at a blood glucose level of 33 mg/dl. He had slightly elevated basal insulin-like growth factor 1 (IGF1) level at 594.84 ng/ml (normal range: 87-460 ng/ml). Chromosome analysis showed a normal male 46, XY karyotype. Lipid profile indicated a low high density lipoprotein (HDL) cholesterol level of 28 mg/dl, a low low density lipoprotein (LDL) cholesterol level of 32 mg/dl and within normal triglyceride level. He was anemic with a hemoglobin level of 8.5g/dl. Nerve conduction studies, and electromyography (EMG) elicited sensorimotor axonal and demyelination neuropathy involving both upper and lower limbs but more marked in the lower limbs. Visual evoked potential (VEP) revealed demyelination of the prechiasmatic optic pathways. Electroencephalogram (EEG) showed a mild degree of generalized neurophysiological disturbance with no epileptiform discharges. Intelligent quotient (IQ) testing by Stanford Binet method gave a level of 59 (mild mental retardation). A psychological evaluation elicited a concentration and memory deficit with feelings of insecurity and self-refusal. Ophthalmology assessment revealed the presence of bilateral hyperopia with no retinitis pigmentosa or cataracts. A mild degree of sensorineural hearing impairment for high frequencies was diagnosed by audiometry.

Patient 2. The sister to patient one, she presented to the genetic clinic based on our request after being told that she has features similar to her brother's features. She was born at term by cesarean section due to transverse lie. Birth weight was 3.2 kgs. She had a within normal developmental course except for delay in speech until 3 years. Around the age of 8 years, her school performance started to deteriorate. She was seen at the genetics clinic at the age of 12 years featuring short stature, tremor, and dental caries. Her height was 112 cm (z-score - 5.1), weight 17 kg (z-score - 6.49), and head circumference 49 cm. She showed similar neurological findings as those of her brother except for the absence of nystagmus. She had pectus carinatum with breast budding. Axillary and pubic hair were Tanner stage 3. The IQ testing by the Stanford Binet method gave a score of 62 (mild mental retardation). A psychological evaluation elicited concentration and attention deficit with preference for easy tasks and feeling of incapability. She showed a markedly exaggerated response to GH provocation test with the GH level reaching a maximum of 117.19 ng/ml during the insulin hypoglycemia test at blood glucose level of 38 mg/dl. Basal insulin-like growth factor 1 (IGF1) level was slightly elevated at 591.53 ng/ml (normal range: 148-495 ng/ml). Chromosome analysis revealed a normal female 46, XX karyotype. Lipid profile gave within normal levels of HDL, LDL cholesterol and triglycerides, and hemoglobin level was 12.9g/dl. Nerve conduction tests, EMG, VEP, EEG, ophthalmological and auditory tests gave similar results to those of her brother.

Figure 1 shows the radiological findings in both patients. Brain computed tomography (CT) showed bilateral basal ganglia calcification, bilateral decreased density of periventricular white matter in the frontal lobes, ventricular dilatation with prominent cortical Sulci, and diffuse brain atrophy. Magnetic resonance imaging (MRI) of the brain showed cerebellar vermis atrophy, in addition to the basal ganglia calcification and white matter demyelination. Skeletal survey showed a thick calvarium, mild degree of platyspondyly of lumbar vertebrae, posterior scalloping of lower lumbar vertebrae, bilateral short second metatarsal, and thinning of lower ribs. Both femora appeared relatively slender with a narrow medullary canal specially in the first patient. Bone densitometry using dual-energy x-ray absorptiometry gave a Z score of – 2.3 SD for the lumbar spine and – 1.7SD for the left hip in the first patient and – 2SD for the lumbar spine and – 1.8SD for the left hip in patient 2. The pedigree is compatible with autosomal recessive inheritance, where the parents are unaffected and first cousins, and the affected are in one generation **(Figure 2)**. The clinical features in the 2 siblings reported here fit the diagnosis of a mild form of CS type 1. The later age of onset, absence of cataracts and retinitis pigmentosa and

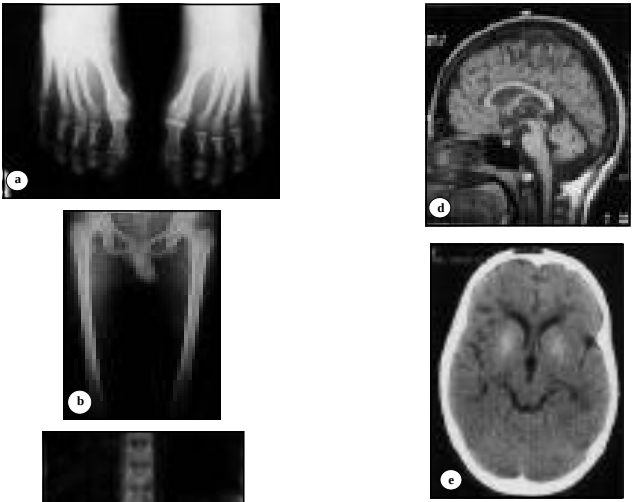

Figure 1 - Radiological findings in both patients. **(a)** Short second metatarsals in patient one. **(b)** Slender femora and narrow medullary cavity in patient one. **(c)** Thinning of the ribs in patient 2. **(d)** MRI brain in patient one showing cerebellar vermis atrophy and white matter demyelination. **(e)** Brain CT in patient 2 showing bilateral basal ganglia calcification, decreased density of periventricular white matter in the frontal lobes, and ventricular dilatation with prominent cortical sulci.

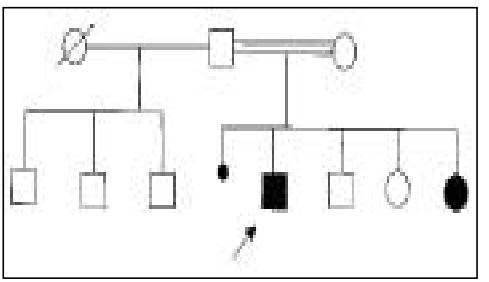

Figure 2 - Pedigree of family with Cockayne syndrome. Arrow indicates the proband.

their generally slower multisystem deterioration could suggest that they represent a new variant with severity ranging between CS type 1 and CS type 3. The boy at age 17 years still runs an acceptable social life, is capable of taking care of himself with the usual daily tasks and has a job of unskilled laborer. His main complaint is tremor. His sister at the age of 12 is still attending a regular school, but she is experiencing difficulty in writing due to tremor.

Discussion. Patients with CS display variable phenotypes for age at onset, symptoms and severity of defects. Phenotypic heterogeneity can be seen among sibs affected by CS in the same family.[4] Clinical criteria are usually useful in most instances to reach a diagnosis of CS. Among 25 patients, the mean age at onset of the symptoms has been reported to be 2 years with a range of 10 months to 6 years.[5] Among 140 cases of CS reviewed by Nance and Berry, poor growth and neurological abnormality were the main criteria required for diagnosis. Other very common manifestations include sensorineural hearing loss, cataracts, retinitis pigmentosa, cutaneous photosensitivity and dental caries. The mean age at death among their cases was 12.25 years, though a few affected lived into their late teens and twenties.[1]

The findings of basal ganglia calcification, demyelination and cerebellar atrophy in the 2 siblings pointed strongly to the diagnosis of CS. Platyspondyly, vertebral body scalloping and metatarsal shortening seen in the radiographs of the siblings have been previously reported among CS patients.[1] New radiological findings include thinning of ribs and the slender femora with narrowing of medullary canals. The latter finding might explain the low hemoglobin level of 8.5g/dl in patient one. We cannot, however, exclude the role of malnutrition in the pathogenesis of the bone changes and anemia in these 2 siblings.

Basal or stimulated GH levels have shown variable results in previous reports of CS, with elevated levels reported in 3 patients in the literature.[1] The 2 siblings in this report showed a markedly exaggerated response to insulin hypoglycemia provocation test, and a slightly elevated basal IGF1 level. The adequate levels of IGF1 could exclude any partial GH insensitivity at the level of IGF-I generation. As CS is one of the families of the rare progeroid syndromes, we looked at GH levels in other progeroid syndromes such as progeria. Data from the literature suggested that elevated GH levels are characteristic of progeria syndrome and that an elevated basal metabolic rate could be the cause of the growth failure seen in this syndrome.[6]

The serum HDL level was low in our first patient, a finding only reported in 2 brothers.[1] However elevated serum cholesterol or lipoprotein levels have been noted in several CS patients in the literature.[1]

Genetic heterogeneity could be responsible for the wide spectrum and variable severity of manifestations in CS patients. Cockayne syndrome can be caused by mutations in 5 different genes with the majority of cases attributable to the Cockayne syndrome group B (CSB). This gene is involved in nucleotide-excision repair (NER), in transcription and transcription-coupled repair by RNA Pol I, II, and III.[3] Xeroderma pigmentosa and trichothiodystrophy are 2 other genetic disorders characterized by defects in the nucleotide excision repair system (NER). The 3 diseases show different clinical phenotypes. Xeroderma pigmentosa is characterized by photosensitivity and increased cancer risk. Trichothiodystrophy and CS share the features of short stature, neurodegeneration and are not cancer-prone.

The main pathology that leads to the phenotype of CS is the progressive neurodegeneration. Three hypotheses have been put forward to link persistent DNA damage to neurodegeneration. The first hypothesis suggests that decreased DNA repair may cause neurodegeneration by impairing the transcription of undefined critical neural genes. A second hypothesis links the defective DNA repair to the triggering of neuronal apoptosis. The third hypothesis implies that persistent DNA damage results in defective neurogenesis.[7] This last hypothesis gained some evidence from studies on mice that pointed to a possible crucial role for the CSB and xeroderma pigmentosa group A (XPA) genes in normal brain development. It was shown that in mice lacking both the XPA and CSB genes, the cerebella were hypoplastic with impaired foliation and stunted Purkinje cell dendrites, and with reduced neurogenesis and increased apoptotic cell death in the cerebellar external granular layer.[8]

Growth hormone has been implicated to have an antiapoptotic effect in several cell types such as cardiomyocytes and lymphocytes.[9,10] If apoptosis plays a role in progressive neurodegeneration in CS, then it could be hypothesized that a high level of growth hormone in our cases had some antiapoptotic effect on neurons resulting in slowing of the progress of neurodegeneration and giving the clinical picture of a mild variant of CS type 1.

Although the genetic defect has been elicited in a large number of patients with CS, the significance of this defect at the cellular and tissue functional levels is still not fully understood. Understanding the functional genomics of CS can help in finding new ways for improving management in these patients.

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