

Clinical Report

Cockayne Syndrome in Three Sisters With Varying Clinical Presentation

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We report three sisters showing the clinical features and investigational findings of Cockayne syndrome (CS). In the rehabilitation unit of Northwest Armed Forces Hospital (N.W.A.F.H.), Tabuk, Saudi Arabia, there was a 12-year-old girl with typical features of CS. The girl had no apparent problems until the end of the first year when growth and developmental delay prompted medical evaluation. Brain CT, bone X-rays, auditory and ophthalmological evaluation confirmed the clinical impression of Cockayne syndrome. Two of her 13 sibs, both sisters, were later found to have the same syndrome. The sisters varied in clinical severity, as two of them had cataracts and early global delay and died early of inanition and infection. The third showed the disease manifestations at a relatively later age, did not have cataract, exhibited milder manifestations of the disease, and remains alive. The parents are not related by any way and the father is married to two other wives with 11 unaffected children. This report documents variable degrees of manifestations in sibs who presumably have the same gene mutation. © 2002 Wiley-Liss, Inc.

KEY WORDS: Cockayne syndrome; Xeroderma pigmentosa; case report; gene repair disorders; autosomal recessive disorders

INTRODUCTION

Cockayne syndrome (CS) is a rare disorder [Ozdirim et al., 1996] first described in 1936 [Cockayne, 1936]. The principal features include: progressive loss of muscle and subcutaneous tissue, short stature, premature aging, senile face, mental retardation, microcephaly, enophthalmos, retinopathy, beak-like nose, hearing loss, carious teeth, relatively large hands and feet, joint contractures, photosensitive dry skin, and thin hair [Cockayne, 1946; MacDonald et al., 1960; Goldsmith, 1997; Meira et al., 2000].

Over 200 cases have been described in the literature [Nance and Berry, 1992]. Inheritance is autosomal recessive [Nance and Berry, 1992; Ozdirim et al., 1996]. The diagnosis is basically clinical, though supportive diagnostic tests are available including computerized tomography (CT) brain, bone X-ray and genetic (DNA) analysis [Nance and Berry, 1992; Lehman et al., 1993; Ozdirim et al., 1996]. The prognosis is poor; most affected children mostly die by the second decade of life [Goldsmith, 1997]. Unfortunately, there is no treatment other than supportive measures [Nance and Berry, 1992; Ozdirim et al., 1996].

A mutation in human DNA repair gene ERCC6 located on the long arm of chromosome 10 has been identified in some CS patients, but the gene mutation alone does not seem to explain the clinical presentation and severity of the symptoms [Troelstra et al., 1993; Rapin et al., 2000]. Prenatal diagnosis is possible [Cleaver et al., 1994]. We report a family whose three affected sibs had a wide variation in clinical severity.

CLINICAL REPORTS

We report these sisters with typical features of CS including the characteristic CT brain scan and other radiological findings.

Patient 1

The eldest girl was born to non-consanguineous parents after a normal delivery with good Apgar score

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and low birth weight. Though she appeared normal at birth; she had early feeding difficulties. She started to lose weight by 4 months of age and was obviously underweight by 1 year. Her weight at 11 years was only 7.3 kg.

She had severe global delay, bilateral corneal scars with poor response to mydriatics, cataracts, and severe sensorineural deafness (Fig. 1). She was able to sit by 3 years and to walk in an awkward manner by 6 years. X-ray showed breaking of vertebrae (Fig. 2). CT brain showed bilateral basal ganglia calcification, diffuse cerebral and cerebellar atrophy with mild ventricular dilatation (Fig. 3). She died at 12 years from emaciation and sepsis.

Patient 2

The second sister was born at term. Birth weight was 2.8 kg. She had a normal course until the age of 2 years when she started to show deceleration in growth and delay in development. She exhibited mental retardation, but did not have cataract and was still ambulatory at age of 10 years. Her general condition has been relatively better compared to her sisters. She started to lose weight at a relatively later age, was able to walk at an earlier age (around 4 years), developed milder joint contractures and did not have cataracts.

Patient 3

The third girl in the family was born with birth weight of 2.1 kg after normal delivery at term. She had the same clinical course as her eldest sister, with weight loss apparent by 8 months of age. Global delay was evident by the age of 3 years, when her weight was only 9 kg. At

7 years of age, she was 8 kg. She was able to walk at around at 6 years and she died at 7 years of age. Table I summarizes the phenotypic variation among the three sisters.

DISCUSSION

These sisters present with the clinical (Fig. 4) and laboratory features of CS, a rare disorder of DNA repair first described by Cockayne in 1936. Cockayne syndrome can be defined by clinical features; at the cellular level, it is caused by a specific defect in the DNA repair system [Lehman, 1982]. After irradiation RNA synthesis is depressed in both normal and CS cells, but it recovers rapidly in normal cells and fails to do so in cells from patients with CS. During transcriptionally active periods, RNA synthesis is impaired in CS cells after exposure to UV light [Lehman et al., 1993]. Both base and nucleotide excision repair systems are normal in CS [Timme and Moses, 1988; Broughton et al., 1995]. Friedberg [1996] proposed that an alternative hypothesis is that CS cells have a defect in transcription affecting the expression of certain genes, which is compatible with embryogenesis but not with normal post-natal development.

Correlation of cellular abnormalities with clinical subgroups has been diverse [Lehman et al., 1993; Itoh et al., 1994]. Out of 52 patients for whom a clinical diagnosis of CS was considered a possibility, 29 showed the characteristic defect of CS cells and 23 had a normal response [Lehman et al., 1993].

Using biochemical complementation analysis of cell lines from different CS patients, 5 complementation groups have been identified [Lehman, 1982]. Stefanini et al. [1996] determined through complementation

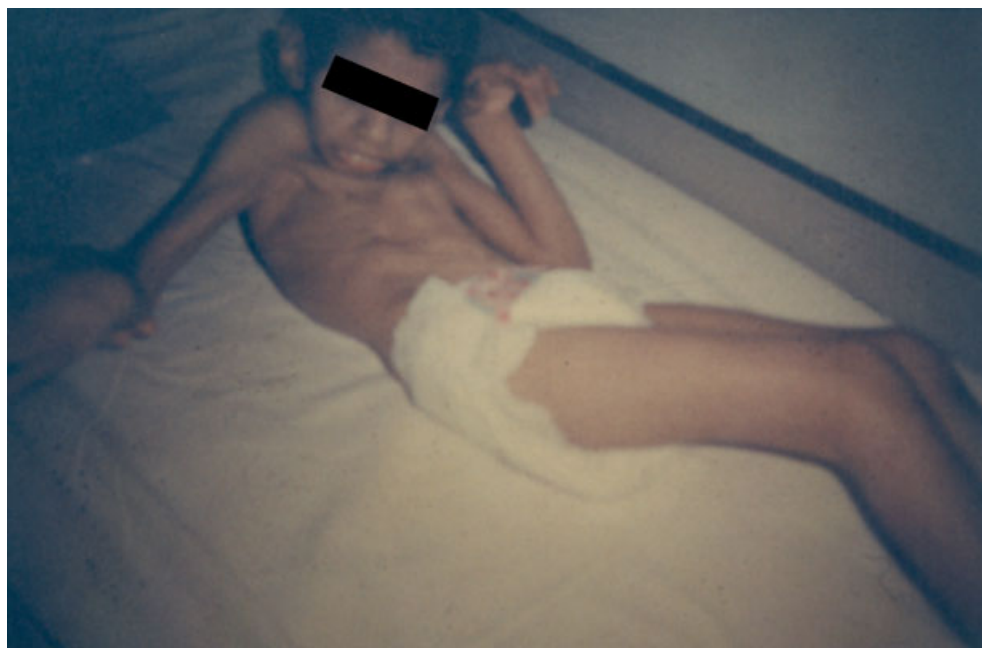


Fig. 1. The eldest sister showing typical clinical features of the syndrome with very emaciated body, microcephaly, enophthalmos and relatively long limbs.

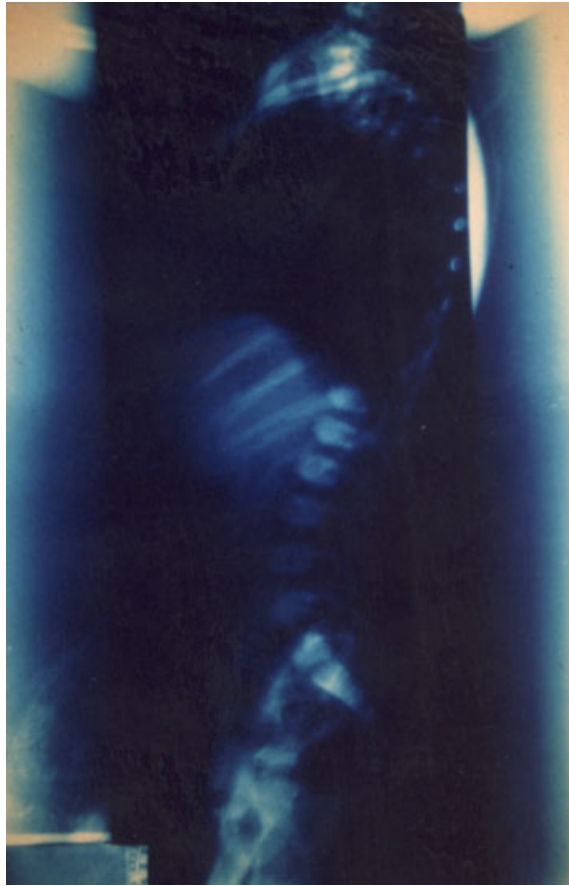


Fig. 2. X-ray bone of the eldest sister showing beaking of vertebrae.

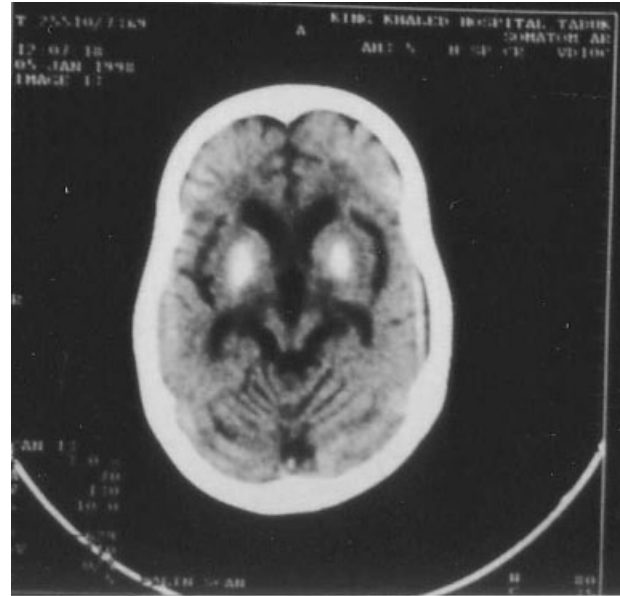


Fig. 3. Computed tomography of the brain of the eldest sister with bilateral basal ganglia calcification, diffuse cerebral and cerebellar atrophy, and mild ventricular dilatation.

studies that about one quarter of CS patients fall into complementation groups CSA, and three quarters into group CSB. These patients usually exhibit CS symptoms only. A few patients have been described with clinical features of CS and the related DNA repair disorder, xeroderma pigmentosum, which includes dry skin, abnormal pigmentation on sun-exposed areas of skin and

propensity to develop skin cancers [Weeda et al., 1990; Broughton et al., 1995; Cooper et al., 1997; Nospikle et al., 1997].

Itoh et al. [1994] reported an UV sensitive syndrome not belonging to any complementation groups of Xeroderma pigmentosa (XP) or CS in two sibs showing biochemical characteristics of CS without typical clinical features [Itoh et al., 1994]. Vermeulen et al. [1993] reported on two unrelated severely affected patients with clinical characteristics of CS, but with chemical defect typical of XP.

Xeroderma pigmentosa has seven complementation groups. Eight patients were recently reviewed and a ninth was summarized [Rapin et al., 2000]. All were found to have Cockayne syndrome-Xeroderma pigmentosa (XP-CS) complex. Despite XP genotype, six of these



Fig. 4. The three sisters in different ages with different degrees of affection as can be seen on their faces, with the one on the left least affected.

TABLE I. Summary of the Phenotypic Variation Among the Three Sisters

Manifestation	Patient 1	Patient 2	Patient 3
Weight at birth	2.2 kg	2.8 kg	2.1 kg
Feeding difficulties	Before 6 months of age	After 2 years of age	Before 6 months of age
Age she started to lose weight	4 months	After 2 years of age	8 months
Age when she started to sit	3 years	7–8 months	3 years
Walking	6 years	4 years	Around 6 years
Global delay	Clear by 1 year of age	After 3 years	Before 2 years
Sensorineural deafness	Yes	No	?
Cataract	Bilateral	No cataract	Possibly not

nine individuals had the typical clinically and pathologically CS phenotype [Rapin et al., 2000]. These observations point out an emerging problem in the definition of this syndrome: should CS be identified according to clinical features, biochemical abnormalities, or genotype? Rapin et al. [2000] and others [Stefanini et al., 1996; Meira et al., 2000] have commented that genotype alone does not predict the clinical presentation, as patients with mutations in the same gene can have widely varying phenotypes, whereas patients with mutations in different genes can have similar presenting phenotypes.

Two other clinical subtypes of CS have been defined, with CSI reflecting the typical presentation with emergence of symptoms around age two and progression over a number of years, and CSII reflecting a more severe presentation with onset either prenatally or in early infancy, low birth weight, ocular pathology including congenital or infantile cataracts, and more rapid progression with death in the first decade [MacDonald et al., 1960; Lowry, 1982; Moyer et al., 1982; Patton et al., 1989].

Type I has been linked to mutations of the CSA gene on chromosome 5, whereas Type II is linked to mutations of the CSB gene on chromosome 10q11 [Rapin et al., 2000]. Pena and Shokeir [1974] described a syndrome named the cerebro-oculo-facio-skeletal (COFS) syndrome, which was reported later by Pena et al. [1978] to be an early infantile form of CS, and recently documented to have a mutation in the CSB gene [Meira et al., 2000]. Seemingly, both CS Type II and some cases of COFS syndrome are due to mutations of CSB gene, and COFS syndrome is viewed as allelic to CSB [Meira et al., 2000].

The presence of cataract early in life is a poor prognostic sign, and a feature of the CSII clinical subtype [Nance and Berry, 1992]. In a review of 140 cases of CS, 22 children developed cataract before 3 years of which only two survived beyond age 7 years [Nance and Berry, 1992]. Two of our three patients (Patient 1 and 3) had features and a clinical course consistent with CS II. Patient 2 had a presentation and course more consistent with CSI, without cataract and with later manifestation of disease symptoms. Although genetic and biochemical studies were not performed in these patients, this family demonstrates that the clinical manifestations and course of CS are not determined purely by the specific gene mutations.

Few patients have been described with clinical features of both CS and XP. Complementation analysis has assigned these patients to XP groups B (*ERCC3*), D (*ERCC2*), or G (*ERCC5*) [Weeda et al., 1990]. The fact that we came across six cases of CS in an area of small population from which the three sisters were living may be related to the high frequency of parental consanguinity that is attributed to the high rate of inbred marriages there. Five of the patients were girls (including these three sisters) and one was a boy. Although patient's survival beyond the second decade is not common [Nance and Berry, 1992; Goldsmith, 1997] (one of our patients died at 7 years of age, while the other died at the age of 12 years), there are reported two adult sibs who were in the fourth and fifth decades of their lives [Miyachi et al., 1994].

Searching the literature indicated that there is no previously described cases of CS where there is a phenotypic heterogeneity in the same family [Nance and Berry, 1992; Miyachi et al., 1994; Ozdirim et al., 1996; Meira et al., 2000]. To the best of our knowledge, this is the first report of three sisters with CS and the first to demonstrate this degree of phenotypic variability of the syndrome within the same family.

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