Title
Cockayne syndrome: The developing phenotype

Journal
American Journal of Medical Genetics Part A, 135A(2)

ISSN
1552-4825

Authors
Tan, Wen-Hann
Baris, Hagit
Robson, Caroline D
et al.

Publication Date
2005-06-01

DOI
10.1002/ajmg.a.30731

American Journal of Medical Genetics 135A:214–216 (2005)

Clinical Report

Cockayne Syndrome: The Developing Phenotype

Wen-Hann Tan,[1] Hagit Baris,[1] Caroline D. Robson,[2] and Virginia E. Kimonis[1]*

[1]*Division of Genetics, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts*
[2]*Department of Radiology, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts*

Cockayne syndrome is a rare autosomal recessive condition comprising microcephaly, "cachectic dwarfism" and progressive neurological degeneration. We present a 21-year-old woman who was not diagnosed with Cockayne syndrome type I until she was 21 years old. Family photographs demonstrated that the phenotype of Cockayne syndrome did not become evident until she was 8 years old. She had severe microcephaly, micrognathia, protruding ears, dental overcrowding with caries, progressive spastic quadriparesis, and severe developmental regression. Her head computed tomography (CT) showed bilateral calcification of the globus pallidus and global atrophy. The purpose of this clinical report is to alert clinicians to the fact that the phenotypic features of Cockayne syndrome may be very subtle early in the course of the disease.

KEY WORDS: Cockayne syndrome; microcephaly; neurodevelopmental regression; basal ganglia calcification

INTRODUCTION

Cockayne syndrome [OMIM 133540 and 216400; OMIM, 2004a,b] is a rare autosomal recessive condition characterized by postnatal growth failure leading to microcephaly and "cachectic dwarfism," as well as progressive neurological deterioration. Although the physical features are well recognized when they are fully developed, Cockayne syndrome can be difficult to diagnose in the early stages.

We present a patient who was not diagnosed with Cockayne syndrome until she was 21 years old because her early craniofacial features appeared relatively normal and developmental regression started only in her late teenage years. Family photographs demonstrated the changing clinical features seen in this syndrome.

CLINICAL REPORT

The patient was born at term following a pregnancy complicated by gestational diabetes, intrauterine growth retardation, and placenta previa. Her birth weight was 2.5 kg (5th centile), birth length was 38.1 cm (below 3rd centile), and head size was described as "small." APGAR scores were 8 at 1 and 5 min.

Although she had a weak suck and was unable to breast-feed, she was able to bottle-feed, and had apparently normal growth. However, when she was around 5 years old, her rate of growth decreased significantly, and she gradually acquired a cachectic appearance. She developed gastroesophageal reflux disease that was treated by Nissen fundoplication and gastrostomy tube placement when she was 20 years old. Menstruation occurred only from age 16 to 19.

Global developmental delay was noted within the first 6 months of life, but she made some progress. She was able to sit unsupported only at 2½ years old, and was able to walk with the assistance of walkers from 4 to 16 years old when she started regressing. She subsequently became wheelchair bound but was able to wheel herself. Since she was 20 years old, she has gradually lost her ability to propel herself and to sit independently.

Her speech was delayed; she spoke her first words at age 3, and achieved a vocabulary of 20 words and 60 signs by age 8. She had a few two- to three-word phrases until she was 18 years old. Since then she has gradually lost all her language, and screaming was her only means of communication. She had previously been sociable, but over the last few years, she has lost interest in her surroundings.

Dysmorphic features were first noted at age 8, when her microcephaly and micrognathia became increasingly prominent. However, it was not until she was 20 years old that the classical features of Cockayne syndrome were recognized, including severe microcephaly, deep-set eyes, protruding ears, hypertrophied alveolar ridges, dental overcrowding, and severe caries. There was no clinical evidence of photosensitivity, which was also denied by history. She had spastic quadriparesis and thoracic kyphoscoliosis (Fig. 1a,b).

When we first evaluated her at 21 years old, her weight was 18.6 kg (3rd centile for a 7½-year-old), height was 118 cm (3rd centile for a 8¼-year-old), and head circumference was 45 cm (3rd centile for a 27-month-old). She had optic atrophy, retinitis pigmentosa-like changes, and was legally blind. Her hearing had previously been normal, but re-assessment was difficult. She had well-developed nipples but had very little breast tissue. Pubic hair was normal (Tanner Stage V), but axillary hair was absent. She had thoracic kyphoscoliosis and atrophic limbs. Neurological examination demonstrated spastic quadriparesis with brisk deep tendon reflexes.

Initial head computed tomography (CT) at 1 year of age had apparently shown "enlarged ventricles" only. However, when she was 20 years old, head CT (Fig. 2) revealed bilateral calcification involving the globus pallidus.

The diagnosis of Cockayne syndrome was subsequently confirmed when ultraviolet (UV) sensitivity assay on cultured skin fibroblasts showed a 3.7 times increase in sensitivity to UV irradiation at the 50% cell survival level.

At the age of 22, the patient was found dead in bed unexpectedly. She had appeared stable the previous night and did not have any prior respiratory infection. An autopsy was not performed.

Sequencing of the ERCC8 and ERCC6 genes (for Cockayne syndrome types I and II respectively) is being pursued, in the

*Correspondence to: Virginia E. Kimonis, Division of Genetics, Children's Hospital, Fegan 10, 300 Longwood Ave., Boston, MA 02115. E-mail: virginia.kimonis@childrens.harvard.edu

Received 5 November 2004; Accepted 14 January 2005
DOI 10.1002/ajmg.a.30731

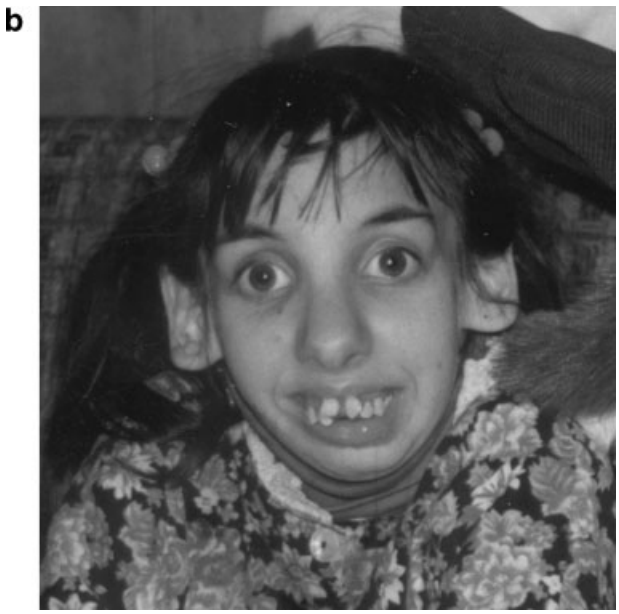

Fig. 1. **a**: Normal-appearing child at 2 years old. **b**: At 16½ years old, illustrating the microcephaly, deep-set eyes, protruding ears, and dental overcrowding, which became increasingly prominent.

hope that more informative genetic counseling may be provided for her siblings and extended family.

DISCUSSION

Since Cockayne syndrome was first described in 1936 by Edward Alfred Cockayne (1880–1956) [Cockayne, 1936], more than 200 cases have been reported. Two main types of

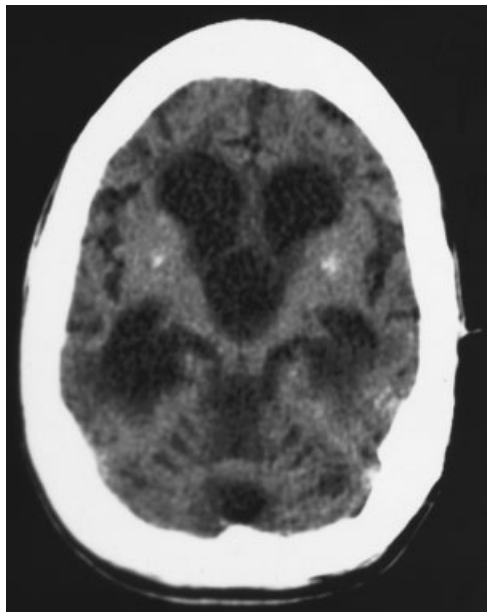

Fig. 2. Head computed tomography (CT) without contrast obtained at 20 years old. This axial image reveals calcifications of the globus pallidus, and ventriculomegaly with prominence of the cerebral sulci and cerebellar fissures, associated with marked ventriculomegaly, consistent with severe global atrophy. The white matter volume appears reduced with periventricular white matter hypodensity. The calvarium appears diffusely thickened.

Cockayne syndrome are recognized—Type I, the "classic" form, and Type II, the more severe neonatal form. Cockayne syndrome was suspected in our patient in view of her facial features, in association with calcification of her basal ganglia. Patients with Cockayne syndrome Type II show minimal, if any, neurological development postnatally, have structural eye abnormalities including cataracts, and rarely survive beyond 7 years of age [Nance, 2004; Spivak, 2004]. Therefore, our patient is likely to have Cockayne syndrome Type I.

Our case highlights the importance of considering Cockayne syndrome in the differential diagnosis of a child with developmental delay, severe failure to thrive and calcification of the basal ganglia because the characteristic craniofacial features may not be noticeable in early childhood, and it behooves the astute clinician to review the child who may have an undiagnosed genetic syndrome on a regular basis over a prolonged period of time, for the answer may lie in the years ahead.

ACKNOWLEDGMENTS

We are indebted to the family of this patient for kindly providing us with the series of photographs and the permission to publish them. We appreciate the assistance of Helen Chan (Division of Genetics, Children's Hospital Boston) with the processing of the photographs. We are grateful to William N. Fishbein, M.D., Ph.D. (Armed Forces Institute of Pathology, Washington, DC) for performing the UV sensitivity studies in our patient.

REFERENCES

Cockayne EA. 1936. Dwarfism with retinal atrophy and deafness. Arch Dis Child 11:1–8.

Nance MA. (Revised September 24, 2003) Cockayne syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle.

1997–2004. Available at http://www.genetests.org. Accessed December 21, 2004.

Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD. MIM Number: 133540. Date last edited: December 8, 2004a. World Wide Web URL: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=133540

Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD. MIM Number: 216400. Date last edited: March 17, 2004b. World Wide Web URL: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=216400

Spivak G. 2004. The many faces of Cockayne syndrome. Proc Natl Acad Sci USA 101:15273–15274.