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Brief Clinical Report: Cockayne Syndrome With Early Onset of Manifestations

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The Cockayne syndrome is an autosomal recessive syndrome of growth failure and characteristic physical and pathological changes. Typically the disorder becomes manifest in the second year of life; growth and development are normal during the first year. We report presumably monozygotic twins with otherwise classic Cockayne syndrome but with a prenatal onset. Several previously described cases seem to represent a similar form of Cockayne syndrome with early onset of growth failure and development delay.

Key words: Cockayne syndrome, prenatal onset, growth failure, neuropathology, ocular manifestations

INTRODUCTION

Cockayne [1936] described a new syndrome of growth failure with retinal degeneration in two sibs. Since then, over 40 patients have been reported with the syndrome. Since no consistent biochemical abnormality has been demonstrated, the diagnosis is made on a clinical basis. Characteristic findings include: onset of growth failure in the second year of life, typical facial appearance with lack of subcutaneous fat and sunken eyes, microcephaly with mental deficiency, retinal degeneration, cataracts, disproportionately long limbs, flexion deformities, and dorsal kyphosis and intracranial calcifications. Some patients have photosensitive skin rash, cryptorchidism, sparse hair, and decreased pupillary response to mydriatic agents [Summitt, 1979]. The disorder presumably is an autosomal recessive trait.

Lowry et al [1971] described two sibs with most of the characteristics of the Cockayne syndrome but an earlier onset of manifestations. Both of these patients were small for gestational age and failed to grow or develop normally in the first year of life.

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Lowry et al [1971] postulated that their patients had a new syndrome. We report twin boys with apparent Cockayne syndrome but with prenatal onset of growth failure.

CASE REPORTS

Patient 1, a twin, weighed 1,540 gm at birth at 39 wk gestation. The pregnancy had been uncomplicated; mother was an 18-year-old primigravida. She and her husband were not consanguineous. Delivery was vaginal with the fetal membranes delivered intact and described as monochorioamniotic. The patient had an occipitofrontal head circumference (OFC) of 27.5 cm and cryptorchidism.

He remained in the nursery for 23 days because of vomiting and inadequate weight gain. This persisted after discharge, and he was readmitted at 2 mo for failure to thrive. The results of chromosome analysis, determination of serum and urine amino acid, rapid plasma reagin, and serum electrolyte levels, of liver and kidney function tests, and of urinalysis were normal. On ophthalmological evaluation the eyes were normal. Skull films showed microcephaly with no intracranial calcifications. Barium swallow examination demonstrated reflux to the upper third of the esophagus.

Growth failure persisted (Fig. 1) and he was cared for at a children's rehabilitation hospital until his death at 3 1/2 yr. At 2 8/12 yr, he had bilateral cataracts and a diffuse loss of retinal pigmentation with a "salt and pepper" appearance retinopathy. Inadequate response to mydriatic agents was also noted. He developed progressive spasticity of the lower limbs with flexion contractures at the knees, kyphosis, sunken eyes, and sparse hair; he was noted to have short palpebral fissures and disproportionately long legs (Fig. 2). Bone age was equivalent to the chronological age. Films of the long bones showed minimal flaring at the ends. No responses were obtained at 100 dB with behavioral observation audiometry. His psychomotor development remained profoundly retarded (Bayley Scales of Infant Development). Just before death he was 60 cm long, weighed 4.6 kg, and had an OFC of 36 cm.

He died of bronchopneumonia. Autopsy showed accessory left renal artery, absence of testes, anomalous high take-off of coronary arteries, microencaphaly (brain weighed 450 gm), severe thickening of leptomeninges, diffuse dysmyelination, and reactive gliosis (Fig. 3). There were multiple small calcospherites throughout the gray and white matter and in the central nuclei. The distribution of the intracranial calcifications was not considered consistent with an intrauterine infection. The inferior surface of the cerebellum was concave and formed part of a posterior fossa leptomeningeal cyst. The cerebellum was atrophic with the atrophy most marked in the internal granular layer.

Patient 2, the twin brother of patient 1, was 43 cm long, had an OFC of 28.8 cm, and weighed 1,810 gm at birth. He was noted to have cryptorchidism and bilateral talipes equinovarus. His course was initially similar to that of his brother. He was also hospitalized at 2 mo for failure to thrive. Results of metabolic evaluation were unremarkable. He also had reflux filling the entire esophagus. He required gavage feedings until 4 mo.

At 8 mo, he was noted to have increasing spasticity of the legs, kyphosis, enlarged knee joints, sparse hair growth, and severe developmental delay. His facial appearance was identical to that of his brother. No responses were obtained at 100 dB with behavioral observation audiometry. His weight at 8 mo was 3,640 gm. He died at home at 8 mo, presumably of aspiration pneumonia. No autopsy was performed.

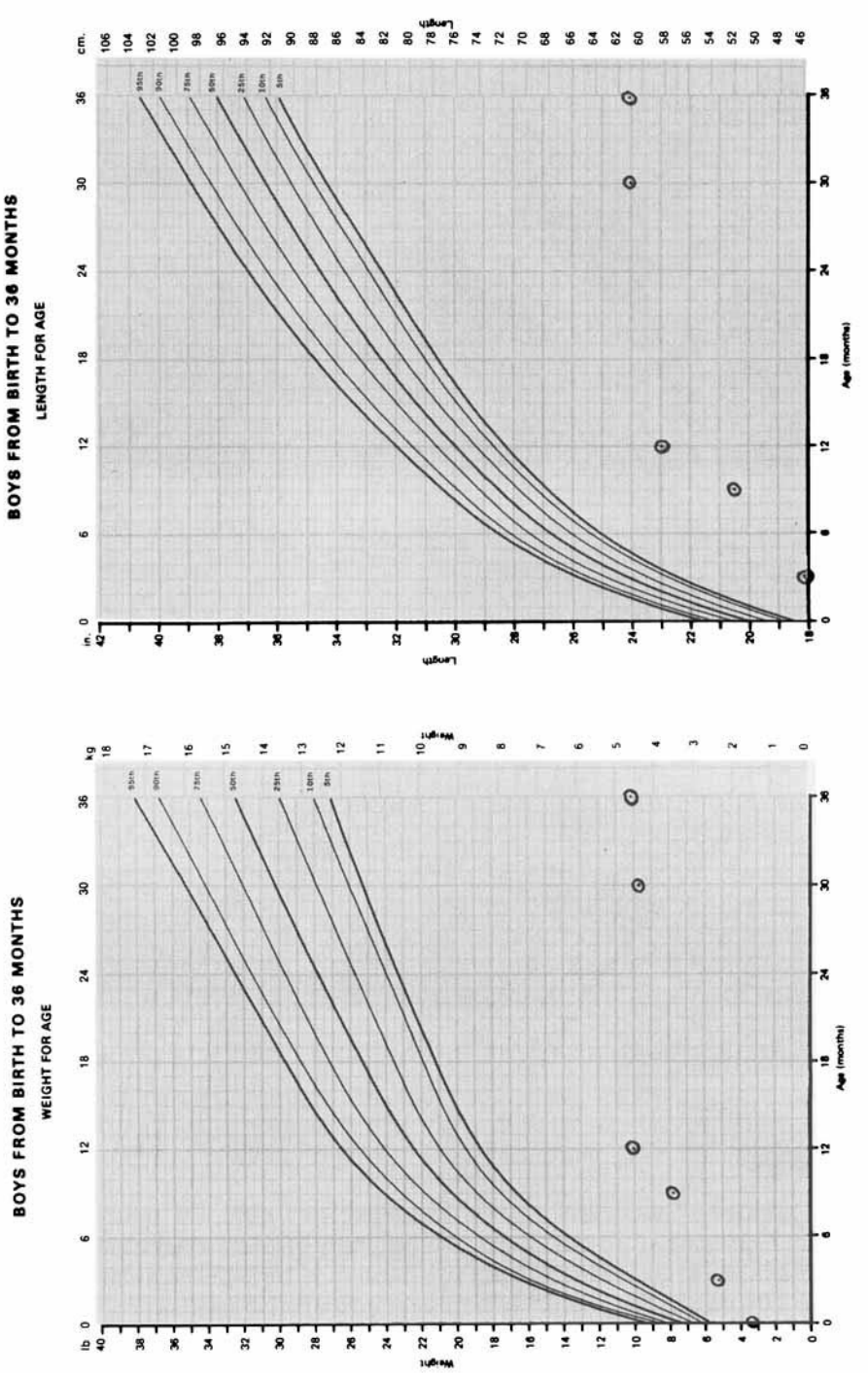

Fig. 1. Growth curves of patient 1 a) weight curve; b) length curve.

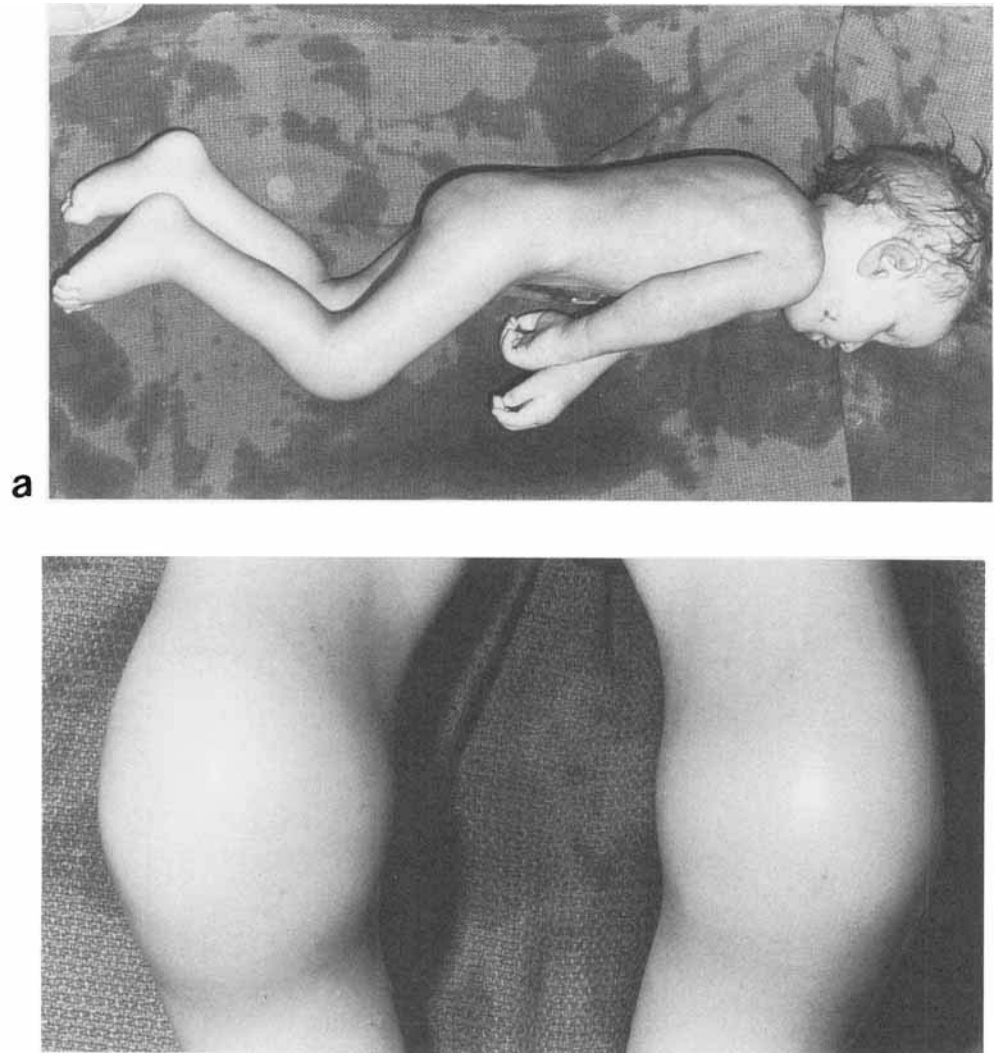

Fig. 2. a,b) Postmortem photographs of patient 1.

DISCUSSION

The presumed monozygotic twins described here meet the criteria for the diagnosis of Cockayne syndrome except for their early onset of manifestations. Two similar patients were reported previously by Lowry et al [1971]. The Table compares the findings observed in our patients with those reported by Lowry et al [1971] and with those seen in the Cockayne syndrome. The similarity of the three groups of patients is striking.

Patient 1, who lived for three yr, finally manifested virtually all of the characteristics of the Cockayne syndrome including all of the eye changes of the syndrome as

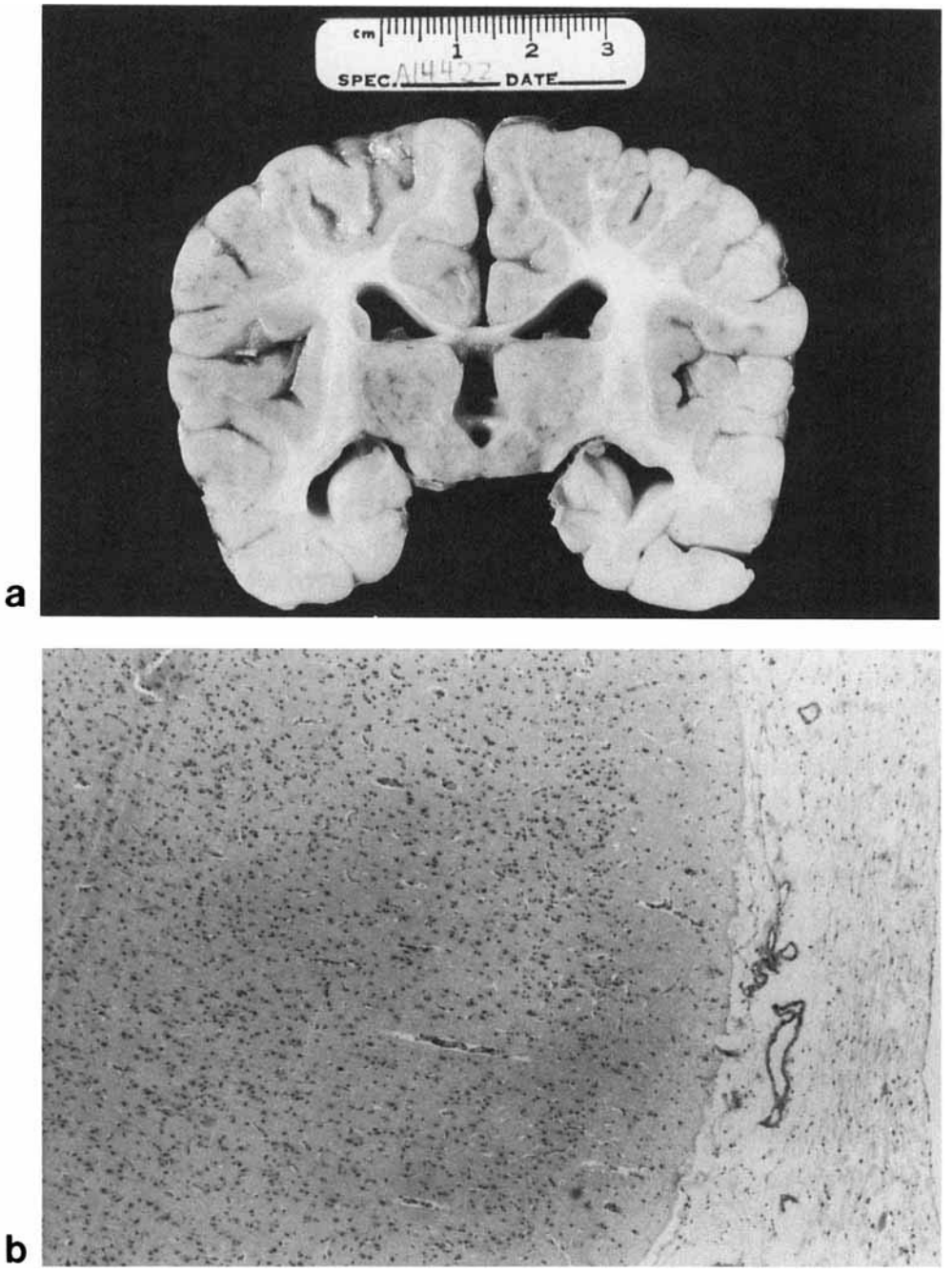

Fig. 3. a) Coronal section of brain, and b) specimen of cortex showing thickening of leptomeninges of patient 1.

TABLE. I. Comparison of Cockayne Syndrome With the Syndrome of the Patients of Lowry et al [1971] and Those Described in This Report

Manifestations	Cockayne patients	Lowry et al	Patients 1,2
Severe mental retardation	+	+	+
Growth failure	+	+	+
Microcephaly	+	+	+
Kyphosis	Frequent	+	+
Cataracts	Frequent	+	+
Deep-set eyes	+	+	+
Joint limitations	+	+	+
Sparse hair	+	+	+
Cryptorchidism	Frequent	+	+
Hearing deficit	Frequent	Not noted	+
Retinal degeneration	+	Not noted	+[a]
Poor response to mydriatics	+	+	+[a]
Birth weight	Normal	Low	Low
Onset of symptoms	Second year	First year	First year

[a]Not noted in our patient 2.

described by Coles [1969]: apparent enophthalmia, short palpebral fissures, cataracts, retinal pigmentation, and inadequate response to mydriatics. Microcephaly, cerebral calcifications, thickened leptomeninges, patchy dysmyelination, and severe atrophy of the cerebellar granular layer are also typical of changes described in this disorder [Moosy, 1967]. Only the early onset of manifestations differentiates our patients from others previously diagnosed as having the Cockayne syndrome.

We think that the findings in our patients lend support to Sugarman's [1973] suggestion that the patients reported as forming a new syndrome by Lowry et al [1971] actually have the Cockayne syndrome, despite their early age of onset.

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