Journal of Korean Medical Science
Vol. 9, No. 1, 74-77 February 1994

Cockayne syndrome : A case with hyperinsulinemia and growth hormone deficiency

Sun-Kyu Park, M.D., Soo-Hee Chang, M.D., Seog-Beom Cho, M.D., Hong-Sun Baek, M.D.*, and Dae-Yeol Lee, M.D.

Department of Pediatrics and Internal Medicine, Chonbuk National University Medical School, Chonju, Korea*

Cockayne syndrome is a rare autosomal recessive disorder of childhood characterized by cachectic dwarfism with senile-like appearance, mental retardation, photosensitive dermatitis, loss of adipose tissue, pigmentary degeneration of retina, microcephaly, deafness, skeletal and neurologic abnormalities. We describe here an 18 year old boy with Cockayne syndrome who had, in addition to the typical features of the disorder, fasting hyperinsulinemia and growth hormone deficiency.

Key Words : *Cockayne syndrome, Hyperinsulinemia, Growth hormone deficiency*

INTRODUCTION

Cockayne syndrome is a rare, autosomal recessive disorder first reported in siblings by Cockayne(1936). The disease is characterized clinically by cachectic dwarfism, cutaneous photosensitivity, loss of adipose tissue, mental retardation, skeletal and neurological abnormalities, and pigmentary degeneration of the retina(Cockayne, 1946 ; Neil et al., 1950 ; Behrman et al., 1983). The life expectancy of patients with Cockayne syndrome is limited. Premature aging is associated with Cockayne syndrome, and it may be differentiated from progeria by the ocular abnormalities and the cutaneous photosensitivity(Neil et al., 1950 ; Behrman et al., 1983). The present paper reports a case of Cockayne syndrome with fasting hyperinsulinemia and growth hormone deficiency.

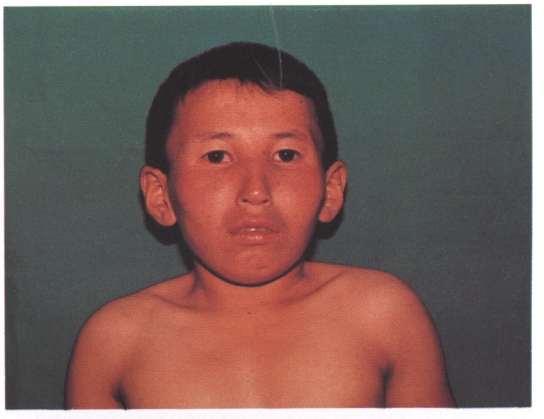
A CASE REPORT

An 18-year-old boy was evaluated for deficient growth and psychomotor retardation. His parents were healthy and not related. Four siblings were born after normal pregnancies. The family history was not contributory. His birth weight was 2720 gm(less than 10th percentile for age). The growth and development of the patient was normal in early infancy except that he never learned to walk(fig. 1A). At 3 years of age, he crawled but did not walk. At about 4 years of age, his growth ceased and his general appearance gradually changed from that of a chubby, healthy child to one of premature aging. At 9 years of age, he walked alone with unstable, wide-based gait. Tendon release surgery was performed on his ankles at 16 years of age.

The patient presented the appearance of a prematurely aged and cachectic dwarf with lordosis(fig. 1B). His body weight was 20 kg, height 109 cm, pulse 90/min and blood pressure 120/70 mmHg. The skull appeared to be disproportionately large with relative dwarfing of the facial structure, but head circumference was only 46.5 cm. Photosensitive dermatitis had been present since one year of age with erythema, and thickened skin over both cheeks and decreased subcutaneous fat. Dark pigmentation was observed on the face and lower extremities. The eyes were sunken and the nose was small and slender. The ears appeared prominent and an audiogram showed bilateral symmetric sensorineural hearing loss. Extensive dental caries

Address for correspondence : *Dae-Yeol Lee, M.D. Department of Pediatrics, Chonbuk National University Hospital, Chonju, Chonbuk, Korea 560-182 Tel : (0652)250-1469*

Fig. 1. A : A 12 month old chubby, healthy child who later developed full-blown Cockayne syndrome.



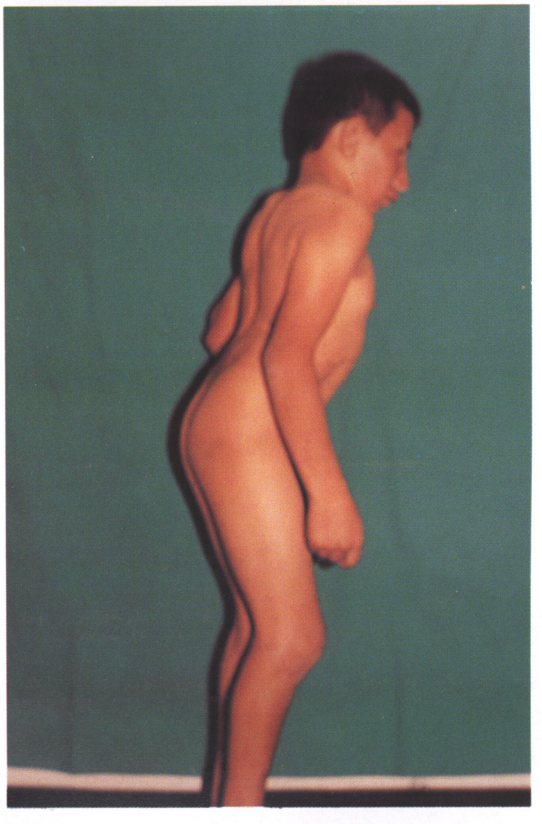


Fig. 1. B : An 18-year-old boy showing the characteristic peculiar face with a senile appearance, sunken eyes, prominent ears and relatively short trunk with lordosis and flexion contractures.

were present and the chest was barrel shaped. Pubic hair(Tanner stage IV) was present but testes were infantile. Flexion contractures involved the ankles, knees and elbows. He had a relatively short trunk and long limbs with large hands and feet. There was diffuse, peripheral mottled retinal pigmentation, retinal vascular attenuation and optic atrophy(fig. 2). Severe mental retardation was present.

Complete blood count was normal. Overnight dehydration urine showed a specific gravity of 1.009, osmolality of 312 mOsmol/kg H_2O with pH 5.0, no protein, no sugar. Fasting plasma glucose was 3.52 and 3.94 mmol/L. Total serum protein was 6.8 gm/dl with 4.3 gm/dl albumin. The ALT, AST, alkiline phosphatase, triglyceride and cholesterol were within normal limits. We checked serum insulin and C-peptide levels twice. On the first visit, serum insulin level was markedly elevated at 309(normal 7 to 24 uIU/ml), with high level of C-peptide(24 ng/ml). Two weeks later, serum insulin and C-peptide levels were 331 and 27, respectively. Peak plasma growth hormone responses to insulin induced hypoglycemia (regular insulin 0.1 U/kg, IV) and arginine provocation test were subnormal(0.1

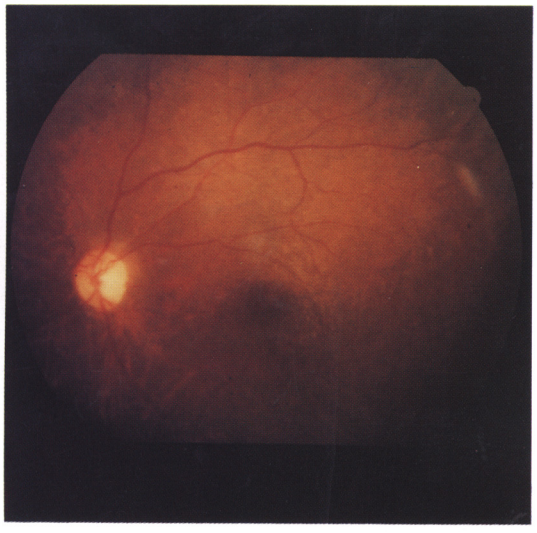


Fig. 2. Diffuse, peripheral mottled retinal pigmentation and optic atrophy.

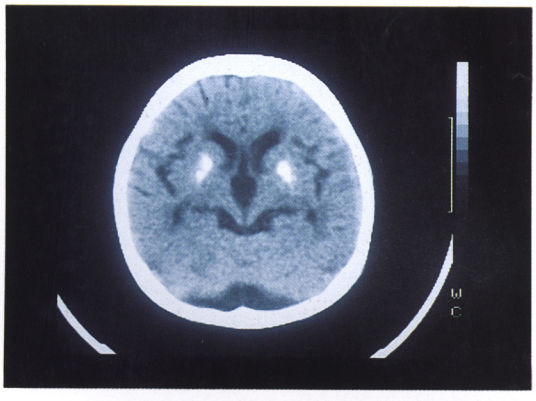


Fig. 3. Cranial CT reveals mild ventricular dilatation and dense calcification in the basal ganglia.

and 1.2 ng/ml). Serum T3, T4, FT4, TSH and cortisol level was within normal limit. Serum insulin-like growth factor I(IGF-I) was 107 ng/ml(normal 163 ± 8 ng/ml). Chromosomal analysis showed a normal 46, XY karyotype. The characteristic X-ray finding was dense intracranial calcification in the region of the basal ganglia(fig. 3). In addition, flattening of the vertebral body and kyphoscoliosis was observed. The bone age was not retarded.

The patient's characteristic facial, neurologic, laboratory and radiologic findings were consistent with Cockayne syndrome.

DISCUSSION

Cockayne first reported the syndrome in 1936 with a report of two siblings who were normal at birth but showed progressive mental retardation and had characteristic senile faces with closely spaced, sunken eyes. Mental retardation, microcephaly, cataracts, sensorineural hearing loss, cutaneous photosensitivity, severe dental caries and renal abnormalities have been reported(Land et al., 1969 ; Jin, 1979)

Craniofacial abnormalities associated with the disease include a relatively small cranium with thick calvarium, salt and pepper retinal pigmentation, optic atrophy, corneal opacity and cataract(Coles, 1969 ; Jones, 1988). Carious teeth are one of the common manifestations in Cockayne syndrome. Patients with Cockayne syndrome frequently develop a photosensitivity dermatitis which can appear in early infancy(Kennedy et al., 1980). Fine hair and disproportionately increased hand and limb size contrasted with a relatively small trunk are common in this syndrome(Kennedy et al., 1980 ; Behrmen et al., 1983). Mild to moderate joint limitation is also frequently observed(Jones, 1988). Renal lesions are relatively new, significant findings in the disease(Ohno et al., 1966 ; Hirooka et al., 1988 ; Sato et al., 1988). Ohno et al(1966) discovered albuminuria with hyalinization of glomeruli, tubular atrophy, and interstitial fibrosis. In our patient, only mild impairment of urine concentrating power was observed. The most prominent radiologic finding is dense intracranial calcification(Alton et al., 1972). In addition, ventricular dilatation, osteoporosis and posterior tapering of vertebral bodies are common abnormalities(Land et al., 1969 ; Bensman et al., 1981).

The endocrine abnormality is one of the rare findings. In our patient, a very high level of fasting serum insulin was found. This finding concurs with Fujimoto's report(1969). Even though hyperinsulinemia existed in our patient, fasting plasma glucose did not drop to the markedly low level seen in idiopathic hypoglycemia and he was asymptomatic. The mechanism of hyperinsulinemia is unknown, but it may be due to peripheral insulin resistance or structural abnormalities of insulin and should be further investigated. We found an abnormal growth hormone response to provocation test and low serum IGF-I level, which suggest that the dwarfism in this disorder may, in part, be due to growth

hormone abnormality.

There are several different human hereditary diseases characterized by defects in the cell's abilities to repair certain kinds of physical or chemical damage to their DNA as in xeroderma pigmentosum and trichothiodystrophy(Hanson et al., 1991). Although patients with Cockayne syndrome are not prone to the development of cancer, a defect in DNA repair following ultraviolet irradiation has been documented(Rainbow et al., 1982 ; Sugita et al., 1987 ; Venema et al., 1990). The life expectancy is limited but patients progress to adolescence and even early adult(MacDonald et al., 1960). Although no cure for Cockayne syndrome is imminent, it may be preventable. The syndrome can be diagnosed prenatally by examining amniotic cells cultured in vitro(Lehman et al., 1985)

REFERENCE

Alton DJ, McDonald P, Reilly BJ : *Cockayne's syndrome : A report of three cases. Radiology 102 : 403-406, 1972.*

Behrman RE, Vaughan VC : *Nelson Textbook of Pediatrics. Philadelphia, WB Saunders Co. pp. 1690-1747, 1983.*

Boraz RA : *Cockayne's syndrome : Literature review and case report. Pediatric Dent 13 : 227-230, 1991.*

Cockayne's EA : *Dwarfism with retinal atrophy and deafness. Arch Dis Child 11 : 1-8, 1936.*

Cockayne's EA : *Dwarfism with retinal atrophy and deafness. Arch Dis Child 21 : 52-54, 1946.*

Coles WH : *Ocular manifestation of Cockayne syndrome. A J Ophthalmol 67 : 769, 1969.*

Fujimoto WY, Greene ML, Seegmiller JE : *Cockayne's syndrome : Report of a case with hyperlipopreteinemia, hyperinsuliemia, renal disease, and normal growth hormone. J Pediart 75 : 881-884, 1969.*

Hansson J, Keyes SM, Lindahl T, Wood RD : *DNA excision repair in cell extracts from human cell lines exhibiting hypersensitivity to DNA-damaging agents. Cancer Research 510 : 3384-3390, 1991.*

Hirooka M, Hirota M, Kamada M : *Renal lesions in Cockayne syndrome. Pediartr Nephrol 2 : 239-243, 1988.*

Jin K, Handa T, Lshihara T, Yoshii F : *Cockayne syndrome : Report of two siblings and review of literature in Japan. Brain Dev 4 : 305-12, 1979.*

Jones KL : *Smith's Recognizable Patterns of Human Malformation. 4th ed. Philadelphia, WB Saundsers Co. pp. 122-123, 1988.*

Kennedy RM, Rowe VD, Kepes JJ : *Cockayne syndrome, an atypical case. Neurology 30 : 1268-1272, 1980.*

Land VJ, Nogrady MB : *Cockayne's syndrome. J Can Assoc Radiol 20 : 194-203, 1969.*

Levinson ED, Zimmerman AW, Grunnet ML, Lewis RA, Spackman TJ : *Cockayne syndrome. J Computer Assisted Tomography 6 : 1172-1174, 1992.*

MacDonald WB, Fitch KD, Lewis IC : *Cockayne syndrome. An heredo-familial disorder of growth and development. Pediatrics 25 : 997, 1960.*

Neil CA, Dingwall MM : *A syndrome resembling progeria : a review of two cases. Arch Dis Child 25 : 213-223, 1950.*

Ohno T, Hirooka M : *Renal lesions in Cockayne's syndrome. Tohoku J Exp Med 89 : 151-166, 1966.*

Rainbow AJ, Howes M : *A deficiency in the repair of UV and gamma ray damaged DNA in fibroblasts from Cockayne's syndrome. Mutation Res 93 : 235-247, 1982.*

Sato H, Saito T, Kurosawa K, Ootaka T, Furuyama T, Yoshinaga K : *Renal lesions in Cockayne's syndrome. Clin Nephrol 29 : 206-209, 1988.*

Sugita K, Suzuki N, Kajima T, Tanabe Y, Nakajima H, Hayashi A, Arima M : *Cockayne's syndrome with delayed recovery of RNA synthesis after untraviolet irradiation but normal ultraviolet survival. Pediatr Res 21 : 34-37, 1987.*

Venema J, Mullenders LHF, Natarajan AT, Van Zeeland AA, Mayne LV : *The genetic defect in Cockayne syndrome is associated with a defect in repair of UV-induced DNA damage in transcriptionally active DNA. Proc Natl Acad Sci USA 87 : 4707-4711, 1990.*