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COCKAYNE SYNDROME IN SIBLINGS (Clinico-Pathological Study)*

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In 1936, Cockayne[1] described two English children with dwarfism, retinal atrophy, and deafness. Similar cases have been reported from various parts of the world, mainly England, France, Belgium, Australia, the United States, Japan, and India[2-9].

This paper presents the first cases of Cockayne syndrome to be reported from Turkey. The clinical findings of both cases (two siblings) and the post-mortem pathological observations of one are given.

Case Reports

Case 1. An 8-year-old boy was seen with the chief complaint of growth retardation. He had been born following a normal pregnancy as the first child of the family. His early development was satisfactory. He sat alone at 10 months, crept at 14 months, and walked at 18 months. Failure to gain weight and unsteadiness of gait appeared at the age of 2 years, and disturbance of speech and lack of response to stimuli appeared shortly afterwards. His physical growth was extremely slow, and at the age of 6 years it appeared to have ceased completely. Increasing clumsiness made such activities as walking and feeding quite difficult; his mental development was also slow. A facial rash as a manifestation of sensitivity to sunlight, visual and hearing loss had been present during the last two years.

Family history revealed that the mother and father were first cousins and that they had three children. The second child was a 5-year-old boy who was normal, and the third child was an 18-month-old girl with symptoms similar to those of our patient. No similar ailment was reported among the family's relatives.

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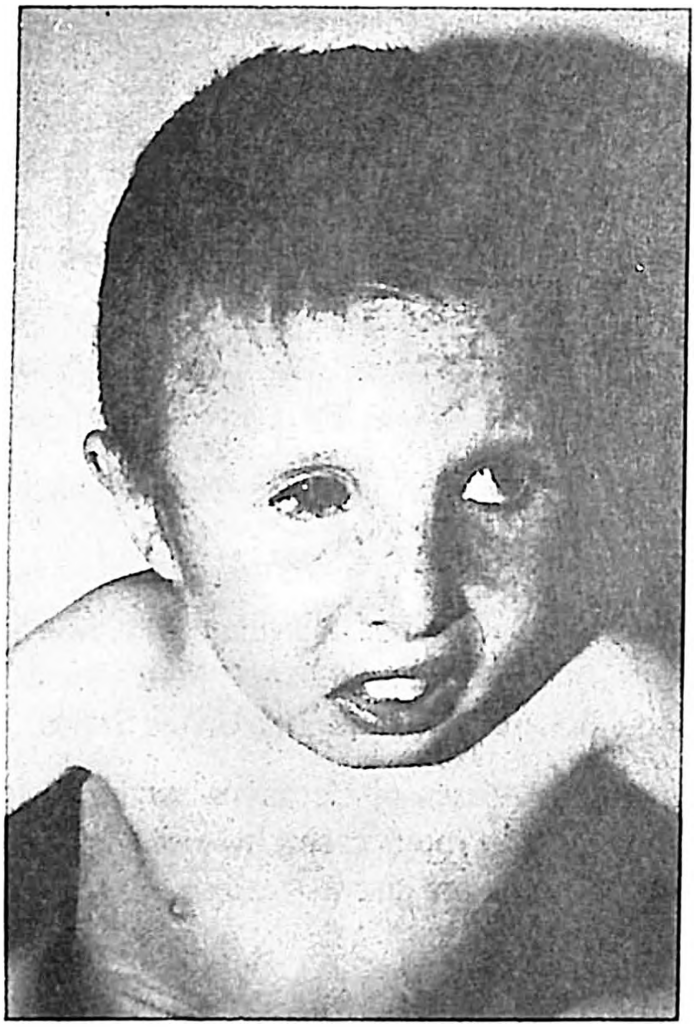

Figure 1.

Facial appearance of Case 1 showing photosensitive dermatitis.

On admission, physical examination revealed a small emaciated child with senile features (Figure 1). He had photosensitive dermatitis, large ears, peaked nose, and carious teeth. The extremities were long, the trunk was short and he had pectus carinatus and kyphoscoliosis. Weight was 8.400 kg, height 84 cm, head circumference 45.5 cm. Eye examination showed isochoric pupils and poor light reflexes bilaterally. Visual activity could not be measured as the child was uncooperative, but it appeared that vision in each eye was limited to light perception and just sufficient to differentiate people. He had congenital cataracts, and the fundi could not be observed in either eye, Audiograms showed neurosensory hearing loss in both ears. He was unable to speak or walk. He had undescended testicles. The rest of the physical findings were normal. Laboratory findings, most within normal limits, are shown in Table I. The patient died of intercurrent infection the ninth day after admission.

TABLE I

LABORATORY FINDINGS IN TWO SIBLINGS WITH COCKAYNE SYNDROME

	Case 1	Case 2
Blood		
Hemoglobin (g/dl)	12.30	10.20
Total leukocytes (/mm^3)	12,000	6,000
Differential count (%)	87	56
Neutropils	87	56
Lymphocytes	9	36
Eosinophils	2	3
Monocytes	2	5
Thrombocytes	Normal	Normal
Urine		
Albumin	Nil	Nil
Reducing substances	Nil	Nil
Microscopy	Normal	Normal
Density	1022	1016
Aminoacids	Normal	Normal
Serum		
Fasting blood sugar (mg/dl)	118	80
Calcium (mg/dl)	10.6	11.2
Phosphorus (mg/dl)	5.7	7.7
Alkaline phosphatase (BU)	7.8	7
Sodium (mEq/l)	143	134
Potassium (mEq/l)	5	4.3
Chloride (mEq/l)	115	101
Carbon dioxide (mEq/l)	13.8	19.8
BUN (mg/dl)	22	15
Total lipids (mg/dl)	800	770
Cholesterol (mg/dl)	205	200
X-ray of the skull	Microcephaly. No calcification	No calcification
Computerized axial tomography (CAT scan)	Calcification + cortical atrophy, ventricular dilatation	Normal
Electroencephalography	Normal	Epileptic activity
Electromyography	Polyneuropathy	Normal
Audiogram	Neurosensorial hearing loss bilaterally	Neurosensorial hearing loss bilaterally

Post-mortem examination. Findings on external examination were as described on clinical examination. Examination of the internal organs showed normal but small organs. The viscerae weighed 50% less than expected for his age. Testes were in the inguinal canal. The brain weighed 700 grams before fixation. The cerebral hemispheres were symmetric, and no malformation was seen. The leptomeninges were slightly thickened and opaque. There was slight cortical atrophy of the fronto-parietal lobes (Figure 2). No pathologic findings were observed of the cranial nerves and vessels; on coronal section there was symmetrical loss of white matter associated with scattered, sharply defined areas of opaque and cheesy discoloration. These spotty changes of white matter were not seen in sections of the cerebellum, brain stem or spinal cord.

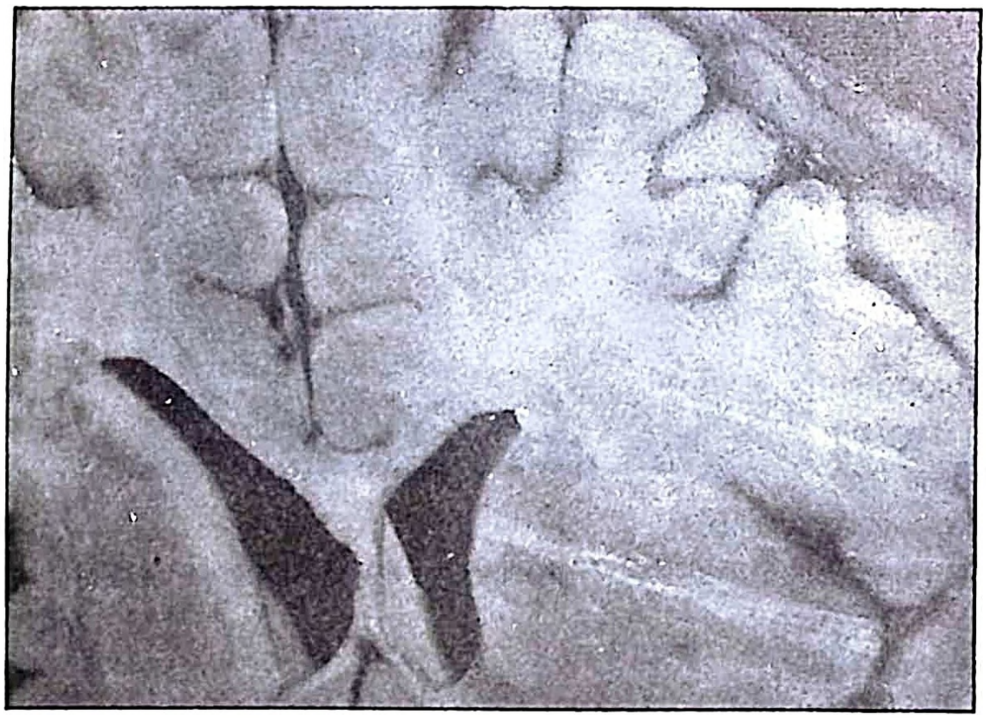

Figure 2.

Coronal section of brain showing slight ventricular dilatation and cortical atrophy.

Microscopic examination. Pertinent findings were bacterial bronchopneumonia, reactive (non-specific) hepatitis, mild neurogenic atrophy of the psoas muscles, marked involutional atrophy of the thymus, glomerulosclerosis, thickening of the basement membranes of glomeruli, tubular atrophy and dilation in the kidney. Testes were rudimentary in appearance which was suggestive of developmental arrest. Punch biopsy of the facial skin was compatible with photosensitivity dermatitis. Sections of the eye were compatible with cataract, but retinal degeneration was not seen. Microscopically, the brain was studied on paraffin and frozen sections. In addition to routine hematoxylin-eosin stain, cresyl violet, toluidine blue metachromasia, oil red and scharlach, luxol fast blue myelin stain, PAS, Prussian blue reac-

tion for iron, von Kossa and alizarin reds were used for calcium. Sections showed slightly thickened leptomeninges without remarkable loss or changes in the cortical neurons. Microscopic findings were confined to white matter of cerebral hemispheres and neurons of basal ganglia. On myelin staining, there was diffuse demyelinization with islands of preserved myelin (Figure 3). There was astrocytic gliosis

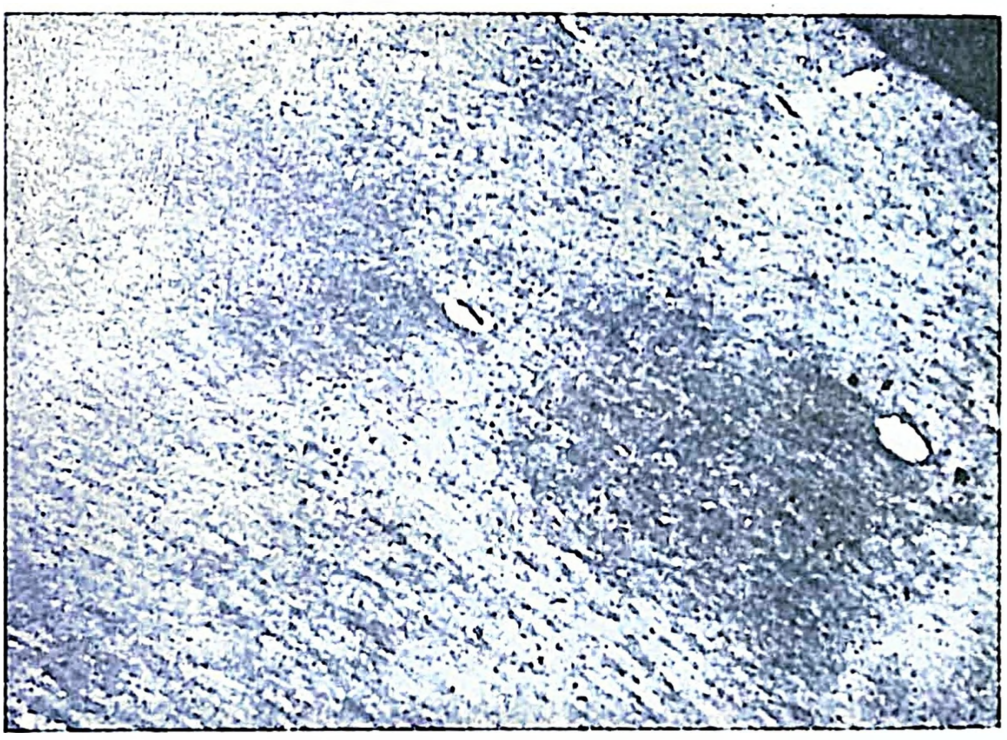

Figure 3

White matter of brain showing diffuse demyelinization with islands of preserved myelin (luxol fast blue × 75).

in the demyelinated areas. No inflammatory cells were seen. There were a few phagocytic macrophages in the perivascular spaces. Sudan stains showed positive staining of the macrophages in the perivascular space and little staining of white matter. Sudanophilic material was soluble in fat solvents and was stainable with PAS. Cresyl violet and toluidine blue metachromasia reactions were negative. Sections of basal ganglia showed loss of neurons and von Kossa and alizarin reds were positive in the neurons and in the walls of the vessels (Figure 4). Hemosiderin reactions for iron were all negative. Sections of cerebellar hemispheres showed decreased granular layer and similar but less extensive involvement of the white matter without mineralization. No involvement of Purkinje's cells or neurons of cerebellar nuclei were seen. There was no evidence of similar involvement of the brain stem or the spinal cord.

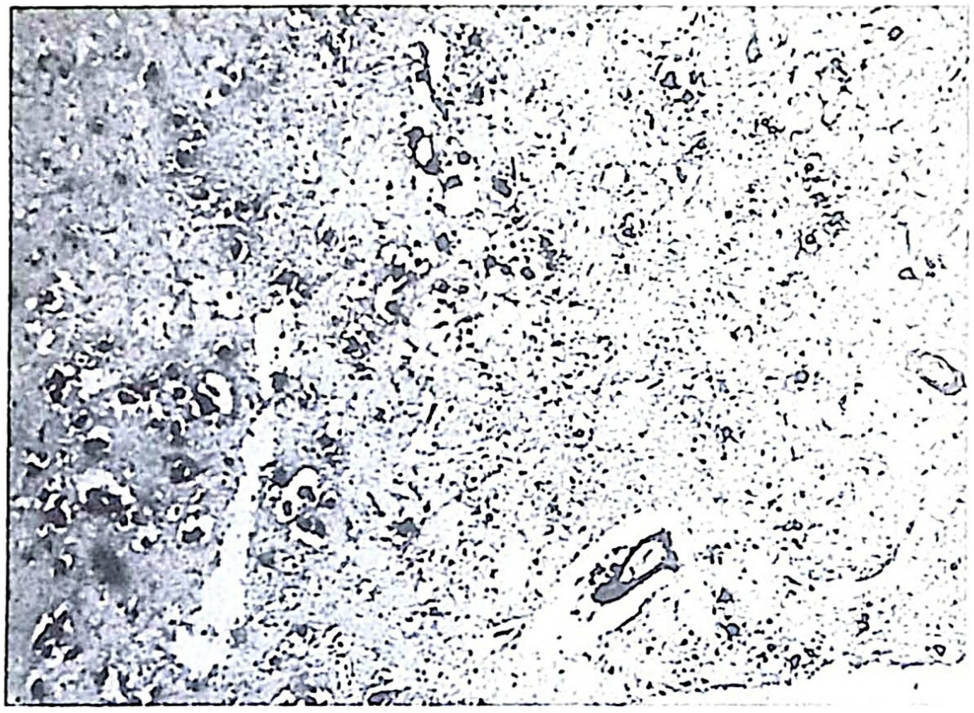

Figure 4.

Basal ganglia showing extensive calcification of both neurons and the walls of the vessels (H EX 250).

Case 2. The younger sister of Case 1 was brought in at the age of 18 months with the complaint of failure to grow. The pregnancy and labor had been uneventful. Early development was normal. The family had noticed after the age of 9 months that her physical and mental progress was extremely slow. She looked small and mentally retarded for her age. Facial appearance was relatively normal except for photosensitive dermatitis. Weight was 8 kg, height 73 cm, head circumference 42 cm. Eye examination revealed isochoric pupils and normal light reflexes bilaterally. Retinitis pigmentosa of the fundi was observed in both eyes (Table II). Her vision was normal bilaterally. Her ears were large and audiogram showed neurosensorial hearing loss in both ears. She was not able to speak or walk.

Discussion

Cockayne syndrome is a rare systemic disorder reported mainly in children. More than 30 such patients have been described to date. Only six instances of siblings and one of twins have been reported. Genetic data are consistent with autosomal recessive inheritance[7,8]. Our cases of a male and a female sibling pair whose parents were first cousins are thus in keeping with the features of autosomal recessive inheritance.

Typical in this syndrome are normal birth and early development followed by progressive changes of the skin, hair, bone, and eyes. Growth retardation and neurologic dysfunction manifest themselves after the first year of life[1,2,7,10,11].

TABLE II

CLINICAL FINDINGS IN TWO SIBLINGS WITH COCKAYNE SYNDROME

	Case 1	Case 2
Dwarfism	+	+
Mental retardation	+	+
Microcephaly	+	+
Retinal pigmentation	–	+
Neurosensorial deafness	+	+
Progeroid features	+	–
Intracranial calcification	+	–
Photosensitivity	+	+
Kyphosis	+	–
Optic atrophy	–	–
Carious teeth	+	–
Large hands and feet	+	–
Hypogonadism	+	–
Large external ear	+	+

In the 8-year-old boy, all characteristic symptoms and findings were noted after normal growth and development for the first two years. Similarly, after normal gestation, delivery, and early development, his 18-month-old sister had shown microcephaly, mental and motor retardation, large ears, neurosensorial deafness, bilateral retinal pigmentation in the fundi and photosensitive dermatitis as of the age of 9 months. However, some of the symptoms noted in her older brother, such as senile appearance, intracranial calcification and polyneuropathy, were not yet fully developed.

The etiology of Cockayne syndrome is unknown. No evidence of biochemical, metabolic, or chromosomal abnormalities or defects of DNA synthesis has been found. When carbohydrate metabolism was tested, some cases revealed a pre-diabetic glucose tolerance curve[4,7,12]. In other patients fasting hyperinsulinemia was observed[12,13]. The relationship of hyperinsulinism and Cockayne syndrome is not clear in these cases.

In our cases, fasting blood sugar was normal and glucose tolerance tests showed no abnormality. Similarly, serum electrolytes and lipid levels were within normal limits.

In differential diagnosis, metachromatic leukodystrophy and progeria should be considered. However, the symptoms and signs found in Cockayne syndrome are not present in progeria, and metachromatic leukodystrophy can easily be differentiated clinically with appropriate laboratory studies[3,5,7,10]. In our first case, autopsy findings indicated bacterial infection, but the thymus showed no dysplasia and the lymph node architecture did not indicate any immunological disturbances. Microscopic findings on the kidney were interesting (Figure 5). The renal lesion in this syndrome has been described in a few patients[7], but the significance of these renal lesions is obscure since renal functional disturbances and hypertension were observed clinically in our cases. Histological examination of the testes revealed underdevelopment for age. This may be related to cryptorchitism, although hypogonadism in such patients has been reported in the literature[1]. Clinical findings of peripheral neuropathy are consistent with slight muscular atrophy. Neuropathological findings have been described in relatively few Cockayne syndrome patients[6,7]. All have the common features of microcephaly, alteration of cerebral white matter with patchy or tigroid demyelinization, and calcification of the small vessels in the basal ganglia, cerebellum and some parts of the cerebrum[14,15]. Neuropathological findings in our cases showed all these features, which are also consistent with a form of sudanophilic leukodystrophy as suggested in the literature[16]. Although consistent association of the neuropathological findings with other organ system involvement is obscure, it may reflect an inborn error of metabolism[1,2,10].

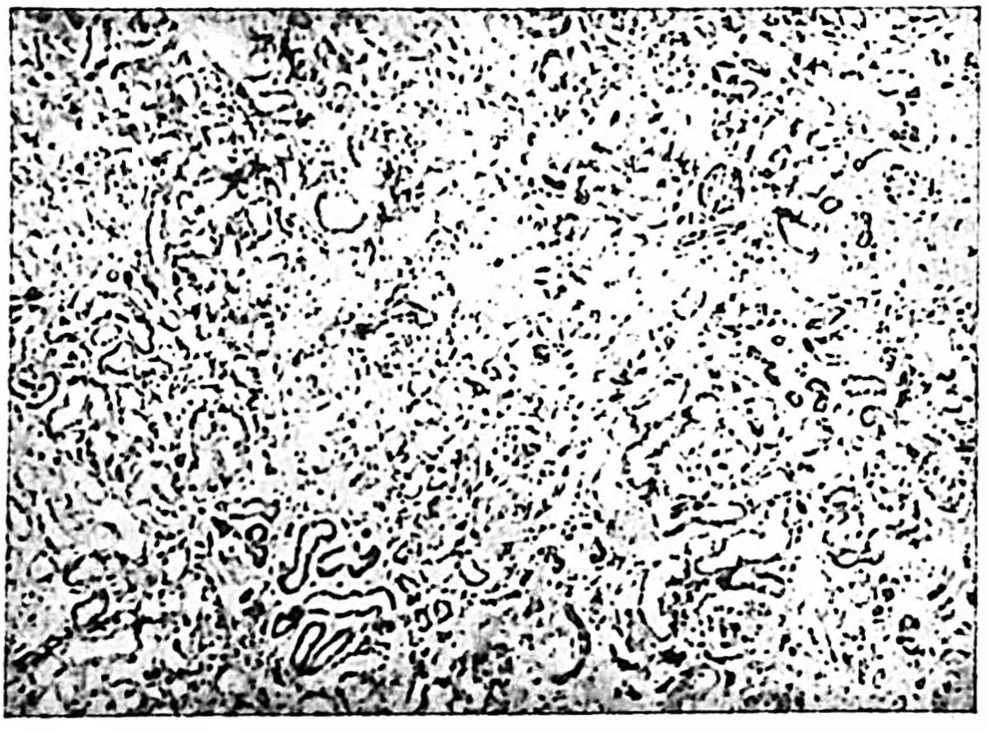

Figure 5

Kidney showing crowded appearance of small sized glomeruli, glomerular and tubular atrophy with mild interstitial fibrosis (H EX 75).

Summary

Clinical and laboratory data on two siblings aged 8 years and 18 months with Cockayne syndrome are presented, the first cases reported in Turkey. Complete post-mortem examination was performed on the older sibling. Pathologic examination of the brain supports the concept that Cockayne syndrome is a form of sudanophilic leukodystophy. Although histologic renal lesions were found, the patient presented no clinical symptoms or signs related to the kidney. The significance of the kidney histology remained obscure.

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