Renal Involvement in 2 Siblings With Cockayne Syndrome

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Renal involvement in Cockayne syndrome is rare and its pathogenesis is yet unknown. We report herein 2 cases (siblings) with Cockayne syndrome type A confirmed by biochemical and molecular assays. The first case was a 13-year-old girl who presented with nephritic syndrome and a rapidly progressive kidney failure. Her younger sister, 7 years old, exhibited hypertension, hyperfiltration, and microalbuminuria. She had hyperreninemia and hyperaldosteronemia without kidney failure or renal arterial stenosis. Renal biopsy, performed the older sister, revealed cystic focal segmental glomerulosclerosis, arteriosclerosis, tubulointerstitial fibrosis, and tubular atrophy. The different clinical phenotypes in the two siblings support the absence of an obvious genotype-phenotype correlation in Cockayne syndrome type A patients. In the older sister, the particular focal glomerular sclerosis and senile lesions assume that kidney disease in Cockayne syndrome may be related to prematurely aging secondary to a defective nucleotide repair.

INTRODUCTION
Cockayne syndrome (CS) is a rare disease, belonging to the family of nucleotide excision repair disorders.1 Renal involvement in CS is rare and its pathogenesis is yet unknown. We report herein 2 siblings with CS complicated by kidney disease.

CASE REPORT
Two sisters born from healthy unrelated parents were diagnosed with CS based on the following findings: growth retardation, severe microcephaly, congenital cataract, progressive neurologic regression, bird-like nose, sunken eyes, limb spasticity, dorsal kyphosis, chest deformity, and narrow pelvis. There was evidence of seizures, deep deafness and blindness, and a motor demyelinating polyneuropathy.

Evidence of a defect in the recovery of RNA synthesis was identified in the older sister: RNA synthesis measured for 1 hour, 23 hours after ultraviolet irradiation of fibroblasts (20 J/m²), was below 20% of normal control. Molecular analysis of CSA/ERCC8 gene revealed homozygosity for the mutation c.400-2A> G. The parents were both heterozygous.

The older sister presented with edema at the age of 13 years. She had hypertension, a moderately reduced kidney function (glomerular filtration rate, 58.77 mL/min/1.73 m²), persistent proteinuria (156 mg/kg/24 h), and hypoalbuminemia (27.8 g/L) without hematuria. She had normal serum calcium level (90 mg/L) and phosphate level (34 mg/L), mild anemia (hemoglobin, 10 g/dL), and normal serum complement. Kidney sizes and differentiation were normal; no stenosis of renal arteries was detected. Blood pressure was controlled by captopril and furosemide. Renal biopsy exhibited different glomerular size with no cell proliferation, nor abnormal deposit. Among 23 visualized glomeruli, 21 were cystic and 2 were collapsed. Two glomeruli showed segmental sclerosis with collapse in one of them (Figure 1). The glomerular basement membranes appeared normal. Few arterioles of the tissue showed hyaline arteriosclerosis, especially
for those located around the glomerulus (Figure 2). Interstitial fibrosis, atrophic and dilated tubules were also noted. Large deposits of immunoglobulin M were detected along the capillary walls, with segmental lesions. Complement C3 was also found in a segmental location along arteriolar walls with weaker deposit of C1q. Death occurred rapidly secondary to end-stage kidney failure.

The younger sister with mild hypertension was 7 years old. Laboratory tests exhibited hyperfiltration (glomerular filtration rate, 135 mL/min/1.73 m²), microalbuminuria, hyperreninemia (77.1 ng/L), and hyperaldosteronemia (1124 pM/L). The kidneys were small but well differentiated. Doppler ultrasonography of the renal arteries and dimercaptosuccinic acid scintigraphy were normal. Captopril was prescribed, hypertension and microalbuminuria were stabilized, but a halving of the glomerular filtration rate was observed during the 4 years of follow-up, without overt kidney failure. Renal pathologic examination result was not available.

DISCUSSION

We described different clinical phenotypes of renal involvement in 2 siblings with CS. This variability supports the absence of an obvious genotype-phenotype correlation in CS. The most common pathology findings were glomerular hyalinization and sclerosis, thickening of glomerular basement membranes, tubular atrophy, and
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Renal involvement in Cockayne Syndrome (CS) can present with a variety of renal lesions. Focal glomerular sclerosis seemed likely to be related to transient and silent hyperfiltration, well demonstrated in the younger sister of our report. Arteriosclerosis and arteriolosclerosis, as in our first patient, were described previously only in 3 patients. 

Renal pathology findings resembled those of an aged kidney. At cellular level, CS cells are DNA-repair deficient. They exhibit a specific defect in transcription-coupled DNA repair, a subpathway of nucleotide excision repair involved in the removal of ultraviolet-induced DNA lesions in actively transcribed genes. Besides, there are defects in basal transcription and in oxidative repair. Recent findings show a mitochondrial dysfunction in cells derived from CS patients. This hypothesis is particularly interesting since mitochondrial deficiencies are believed to be important in the aging process.

At molecular level, our patients had mutations in the CSA gene. The CSA protein is required for recruitment of other factors in the nucleotide excision repair subpathway. It is also involved in the response to oxidative stress and contributes to prevent the accumulation of various oxidized DNA bases in vivo. Defect in this protein leads to apoptotic response and can explain both neurologic degeneration and senile lesions of kidneys.

In conclusion, CS patients should be monitored for kidney disease. Senile renal lesions reported in the older sister of this report, suggest a possible relation between kidney disease in CS and premature aging, as a consequence of a defective nucleotide repair. Variable renal phenotypes, demonstrated here, and its pathogenesis will be better understood with mouse models.

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**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


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