Renal failure due to tubulointerstitial nephropathy in an infant of cranioectodermal dysplasia

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Abstract. Cranioectodermal dysplasia (CED) is a rare autosomal recessive disease with characteristic craniofacial, skeletal, and ectodermal derived tissue abnormalities. In this disease, tubulointerstitial nephropathy (TIN) has been reported as one of the life-threatening combinations. Here we report a sporadic case of CED who showed signs of renal failure during perinatal period. Renal biopsy at 6 months old revealed TIN consisting of marked interstitial fibrosis with inflammatory cell infiltration accompanied by scattered tubular atrophy. Glomeruli were often sclerosed and others showed prominent immaturity; the findings are supportive of progressive deterioration of renal function in this infant. This case suggests that TIN in CED can occur during the fetal period and progress rapidly, leading to end-stage renal failure within infancy.

Introduction

Cranioectodermal dysplasia (CED) is a rare autosomal recessive disorder characterized by external features such as dolichocephaly due to sagittal suture synostosis, rhizomelia, brachydactyly, short narrow thorax, sparse slow growing hair and hypodontia [1]. In addition to these ectodermal defects, renal symptoms can be additionally associated with CED and the renal failure is one of the life-threatening conditions in this disorder [2]. Previous reports have described that symptoms of renal failure in CED develop during early childhood and the renal involvement in CED consists of tubulointerstitial nephropathy (TIN) [2].

Here we report on clinicopathological features of a patient with CED who developed renal failure prenatally. The cause of the renal failure is attributable to severe TIN including a marked interstitial fibrosis and inflammatory cell infiltration. In addition, the findings suggested a cessation of glomerular maturation during fetal kidney development. This case represents the first report of renal failure in infancy in CED syndrome.

Case report

This female infant, the first child of unrelated Japanese parents; the mother of 27 years old, was born at 37 weeks gestation by elective cesarean section, weighing 3.37 kg. The pregnancy was established following ovulation induction. Oligohydramnios was diagnosed prenatally at 28 weeks by ultrasonography. After birth, dyspnea developed due to pneumothorax and pulmonary hypoplasia, requiring mechanical ventilation for 6 days.

The patient was noted prominent dolichocephaly, narrow short thorax and short limbs (Fig. 1) at birth. Moreover, blood examination revealed elevated blood urea nitrogen (24 mg/dl) and serum creatinine (1.8 mg/dl) at day 1. She showed hematuria and mild proteinuria (30—50 mg/dl) with the presence of low molecular weight proteinuria (urinary β2-microglobulin 75.7 mg/l). Renal ultrasonography and MRI demonstrated normal kidney size without apparent hydronephrosis. In addition, no abnormalities in lower urinary tract including vesicoureteral reflux were demonstrated by voiding cysturethrography. A technetium-99m MAG3 scintigraphy showed extremely low effective renal plasma flow in both kidneys. According to characteristic external features including dolichocephaly due to sagittal craniosynostosis, short limbs, sparse hair, narrow short thorax and polysyndactyly, this patient was received a diagnosis of the syndrome

cranioectodermal dysplasia. Esotropia was found, but ophthalmologic studies including fundoscopy revealed no retinal involvement at the stage of 15 months of age.

She needed oral base therapy for the corection of mild acidemia. Tube feeding was started at 5 months old to achieve her growth potential and to prevent frequent vomiting with gastroesophagial reflux. At the age of 9 months, peritoneal dialysis was started with uncontrollable hyperkalemia. Peritoneal dialysis therapy has been safely maintained with a favorable body weight gain and she showed the 10th percentile in body height during growth. So far, motor development in this patient has been significantly delayed with roll-over at 7 months old. She was unable to sit without support at 15 months of age. Although she had afebrile seizures at age 12 month, the electroencephalogram showed no abnormalities and the seizures were not recurrent. Her mental development was not delayed, but her overall development status corresponded to 12 months of age when she was 15 months of age.

Kidney wedge biopsy was performed at 6 months old. Predominantly, extensive interstitial fibrosis with focal inflammatory cell infiltration and scattered tubular atrophy and casts were observed (Fig. 2A). Medullary cysts were absent and thickened tubular basement membranes were not prominent. Glomeruli were often

sclerosed globally or segmentally; the others indicated significant immaturity. Ultrastructural observation demonstrated adjoining cuboidal podocytes containing extensive biosynthetic organelles in the cytoplasm with the findings of immaturity of foot-process formation and remanence of apical junctional complex (Fig. 2B). No significant deposition of immunoglobulins and complements in glomeruli and tubulointerstitium was demonstrated. Immunohistochemistry using specific antibodies demonstrated that infiltrating cells in tubulointerstitium were mainly composed of CD4- and CD8-positive T lymphocytes and CD68-positive macrophages (data not shown).

Discussion

CED is a very rare autosomal recessive disorder (15 cases in literature) first reported by Sensenbrenner et al [1, 3-5]. In Japan, Tamai et al. reported 2 siblings of this syndrome including the case who died of respiratory falure as a result of thoracic hypoplasia shortly after birth [6]. Here we report a sporadic case of this syndrome who developed end-stage renal failure within infancy.

External manifestations in this patient are very consistent with a diagnosis of this syndrome, except for the absence of retinal involvement and the presence of significant motor development delay. Due to the fact that retinal involvement has been described in some previous cases [7, 8], we must continue to render attention to eye symptoms secondary to retinitis pigmentosa in later life of this case. Developmental delay is not a characteristic feature in this syndrome, although a few reports described the presence of mild psychomotor delay [2, 9]. The etiology of the delay has been obscure. We consider that motor development delay in this patient might be secondary as a result of the uremic state developed because of chronic renal failure since birth. Furthermore, frequent hospitalization in addition to her extremely short limbs might also affect the dalay.

In this patient, the signs of renal failure appeared during the perinatal period and the kidney function deteriorated rapidly, leading to end-stage renal disease (ESRD)

within infancy. Previously, Savil et al first reported 4 patients with CED who developed progressive renal failure [2]. They described that the nature of renal involvement in this syndrome is insidious and progresses to ESRD between age 3 and 11 years. Another report described a 6 year old CED patient who also developed ESRD [10]. Compared to these cases, our patient presented signs of renal failure already during the perinatal period. Oligohydramnios and pulmonary hypoplasia were noted in this patient, suggesting the presence of renal impairment in the fetal period. This finding may suggest that renal involvement in CED could progress from a stage of fetal kidney development.

Histopathologic examination of renal tissue at 6 months of age revealed TIN. In tubulointerstitium, a marked fibrosis and tubular casts were observed with scattered infiltration of T lymphocytes and macrophages. In addition to tubulointerstitial changes, the kidney of this patient showed significant predisposition of glomerular immaturity. This finding may reflect a disturbance of late glomerular maturation caused by significant tubulointerstitial damage in this syndrome [11].

The cause of renal impairment in CED has not been resolved. The renal histologic findings showing progressive TIN resemble the findings in nephronophthisis [12]. In addition, infantile type of nephronophthisis, which shows

rapid deterioration of renal function after birth and reaches ESRD within the first 2 years of life, has been reported [13]. However, the affected skeletal and ectodermal structrures in CED are distinct from the extrarenal associations in nephronophthisis and Senior-Loken syndrome. Recently these diseases have been considered as cilia-related disorders [12, 14]. It is of note that skeletal patterning defects including polydactyly were caused by mutations in the polycystic kidney disease gene Tg737, a mouse homologue of Intraflagellar transport (IFT) gene [15, 16]. The underlying genetic defect must be further validated to define the defects of tubulointerstitial components. This case illustrates the wide spectrum of age of progression to ESRD and the possible onset of tubulointerstitial injury during renal ontogenesis in this syndrome.

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Figure legends.

Figure 1. Roentgenography at day 1 showed dolichocephaly, short narrow thorax and short upper limbs (left panel). Dolichocephaly due to sagittal suture synostosis was demonstrated by 3-dimensional computed tomography (right panel).

Figure 2. (A) Light microscopic findings of the renal biopsy specimen. There was a marked interstitial fibrosis and inflammatory cell infiltration (asterisks). Tubular atrophy and casts were also scattered. Glomeruli were occasionally sclerosed (arrowheads), and some glomeruli showed significant immaturity (arrows). (B) By electron microscopy, podocytes showed extensive biosynthetic organelles in the cytoplasm. Foot-process formation was immature showing the remanence of apical junctional complex.

Fig. 1

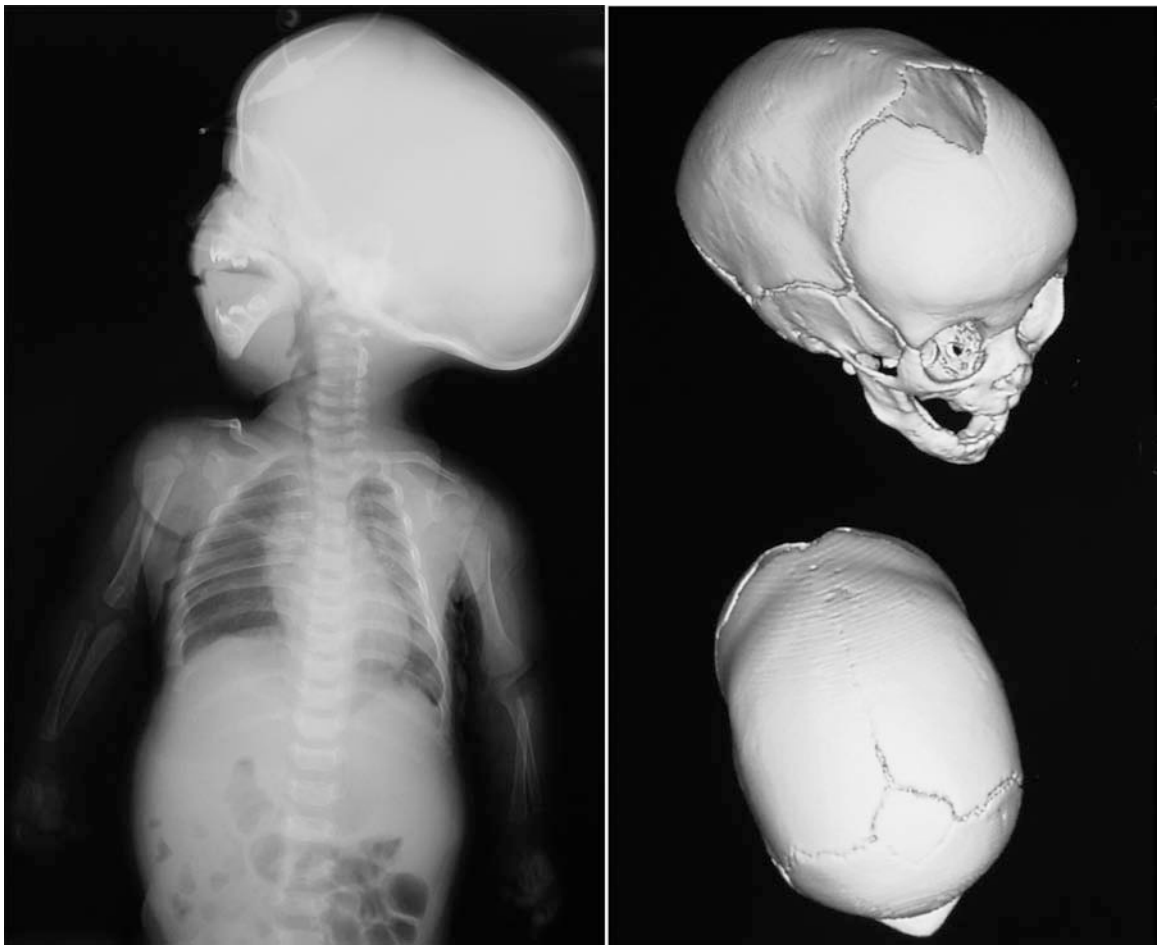

Fig. 2