An Isolated Case of Nephronophthisis:
Medullary Cystic Disease without Typical Onset

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A 16-year-old girl with renal failure was transferred to our hospital for an extensive renal examination. Computerized tomography and ultrasonography showed multiple small cysts throughout the medulla of both kidneys. Histological findings revealed tubular atrophy and dilatation and marked periglomerular fibrosis, all of which were compatible with nephronophthisis. Her development and growth were normal. A prior urinalysis, as well as her symptoms and family history were not helpful for making a diagnosis. As early diagnosis of nephronophthisis is difficult in some cases, more detailed screening is needed for children and adolescents.

(Key words: medullary cyst, renal failure)

Introduction

Nephronophthisis-medullary cystic disease complex (nephronophthisis) is characterized by juvenile onset, progressive renal damage, medullary cysts, retinal degeneration and inheritability (1). It is considered an important cause of renal failure in adolescents and young adults (2-4), but its pathogenesis and actual incidence in Japan are unknown.

We present a young female patient with end-stage renal failure for whom an early diagnosis of nephronophthisis was difficult because her growth was normal and she had neither a family history nor typical symptoms of renal disease. Isolated cases of nephronophthisis and the need for a more detailed urinary screening test are discussed.

Case Report

The patient, a 16-year-old girl, showed normal growth and development. Her parents are first cousins, but there is no family history of renal disease. She was admitted to a local hospital because she had suffered general fatigue for several months. Until that time, she had displayed no evidence of proteinuria or hematuria nor did she have polydipsia, polyuria or enuresis. Physical examination showed a height of 157 cm, body weight of 57 kg and blood pressure of 110/60 mmHg with a regular heart rate of 66 beats per minute. No edema was present in her face or extremities. Neurological examination results were normal. Visual acuity was normal, and an ophthalmological assessment found neither retinal degeneration nor optic atrophy. Hearing loss was not found.

Laboratory data were as follows: white blood cell count, 7,800/μl; red blood cell count, 345 x 10^6/μl; hemoglobin, 10.4 g/dl; hematocrit, 30.9%; platelet count, 33 x 10^9/μl; serum total protein, 8.1 g/dl; albumin, 5.2 g/dl; aspartate aminotransferase, 12 IU/l; alanine aminotransferase, 14 IU/l; lactate dehydrogenase, 278 IU/l; γ-glutamyl transpeptidase, 5 IU/l; creatinine, 10.5 mg/dl; blood urea nitrogen, 133.7 mg/dl; alkaline phosphatase, 545 IU/l; C-reactive protein, 0.8 mg/dl; sodium, 133 mEq/l; potassium, 3.9 mEq/l; calcium, 9.6 mg/dl; phosphorus, 8.7 mg/dl; serum high sensitivity parathyroid hormone (HS-PTH), 11,000 pg/ml (normal range 160-520); serum intact parathyroid hormone (i PTH), >1,000 pg/ml (normal range 15-50); serum erythropoietin, 16.7 mU/ml (normal range 8-36); C3, 93 mg/dl; C4, 41 mg/dl; CH50, 53 U/ml; rheumatoid arthritis test, negative; antinuclear antibody, ×40; and anti-DNA antibody, ×80. Urine volume was 1,200 ml/day and her urinary protein excretion was 0.3 g/day. Urinalysis showed proteinuria (+) and hematuria (+). The sediment showed 1 to 4 red blood cells per high-power field and no casts. Urine specific gravity was 1.005, and repeated urine cultures were negative. Hemodialysis therapy was begun under the diagnosis of renal failure. She was transferred to our department for an extensive renal examination. Ultrasonography and computed tomography (CT) indicated a normal liver. There were multiple cysts...
with diameters of up to 10 mm in the medullary and cortico-medullary regions of both kidneys (Fig. 1). Several cortical cysts also were present. Atrophy of the kidneys was not apparent (right 9.2 x 3.8 cm, left 9.4 x 3.8 cm). Ultrasonography of the neck revealed 2.1 cm x 1.3 cm and 1.0 cm x 0.8 cm masses in the upper left and lower right lobes of the thyroid. A renal biopsy showed that about half of the glomeruli had periglomerular fibrosis with variable severity of hyalinosis and hypercellularity and that the rest appeared obsolescent (Fig. 2). Extensive tubular atrophy and interstitial fibrosis with chronic inflammatory infiltrations were noted. Cystically dilated tubules were present in places. No medullary cysts were found in the renal specimen. Findings of an immunofluorescent study were nonspecific.

During a one-year follow-up the patient has received maintenance hemodialysis and attends school as previously. On receiving oral calcitriol therapy, her parathyroid hormone levels decreased (i PTH 340 pg/ml, HS-PTH 5 1,000 pg/ml). She is now awaiting kidney transplantation.

**Discussion**

Juvenile nephronophthisis was first described in 1951 by Fanconi et al (1) and it is clinically characterized by inheritability, juvenile onset, polyuria, polydipsia, anemia, growth retardation and progressive renal damage. In the four decades since, a number of terms have been used to describe this condition: medullary cystic disease, cystic disease of the renal medulla, familial juvenile nephronophthisis, salt-losing nephritis, renal-retinal dysplasia and Fanconi’s nephronophthisis, which now are recognized as referring to the same entity that is characterized by apparent familial transmission and cyst formation in the medullary and cortico-medullary regions of the kidney. Gardner (2) has proposed as subgroups of this disease: isolated cases (15%), juvenile nephronophthisis (50%), renal-retinal dysplasia (17%), and adult-onset medullary cystic disease (18%). Juvenile nephronophthisis and renal-retinal dysplasia are recessive inherited diseases, and adult-onset medullary cystic disease is a dominant inherited variant. On the basis of the inability to concentrate urine or renal sodium loss, polydipsia, polyuria and enuresis are the earliest presenting complaints in more than 80% of the reported cases (5). Growth retardation is seen in most patients who are more than 2 or 3 S.D. below the mean height for their ages (6, 7). A family history of renal disease, the patient’s symptoms, and growth retardation are important for an early diagnosis, but the ultimate diagnosis is made by the demonstration of the characteristic medullary or cortico-medullary cysts (2, 3). Because our patient had no family history, typical symptoms, or growth retardation, an early diagnosis of nephronophthisis could not be made. Urinalysis usually is not helpful in diagnosing this disease, and neither proteinuria nor hematuria were found in this patient at a school screening examination, although both were found upon hospital admission as a result of renal failure.

Various diagnostic imaging modalities have been used to confirm the diagnosis of nephronophthisis. Intravenous pyelograms show shrunken and poorly functioning kidneys that are indistinguishable from the small kidneys produced by other chronic renal diseases. Renal angiography is more specific and the investigation of choice. Mena et al (8) identified renal cysts in 4 of 5 cases during the nephrogram phase, but this test is invasive and inappropriate as an initial procedure. Ultrasonography and CT have been recommended because both are sensitive and noninvasive (7, 9). In cases in which renal cysts are too small to be detected, thin section CT (1 to 2 mm thickness) is reported to be helpful (10). CT and ultrasonography detected several medullary and cortico-medullary cysts in our patient, and renal biopsy showed severe interstitial changes and periglomerular fibrosis. Diminished ability to concentrate urine may precede any documentable reduction in glomerular filtration as measured by endogenous creatinine clearance (2). When the patient was admitted to our hospital, her ability to concentrate urine could not be used as a diagnostic factor.
because of renal failure, but the finding of imaging modalities was typical of nephronophthisis. We did not detect the presence of medullary cysts in the renal biopsy specimen, but the atrophy and dilatation of the tubules, as well as periglomerular fibrosis are considered typical of this disease.

Our patient was considered to have an isolated case of nephronophthisis, because her grandparents, parents, and brother had no history of renal disease. The family history prior to her grandparents, however, was not clear, and the consanguinity of her parents suggests the possibility of recessive inheritance. Isolated cases may indicate new mutations (2), but recessive inheritance cannot be ruled out. Associated nonrenal anomalies, including tapetoretinal degeneration, retinitis pigmentosa, central nervous system abnormality and skeletal anomalies, usually are present in autosomal recessive diseases (6, 11–13). Although the clinical features of isolated cases, including the time of onset, have yet to be clarified, our patient’s case suggests that normally developing patients who have no family history, typical symptoms or nonrenal abnormalities may be candidates for nephronophthisis.

Nephronophthisis-medullary cystic disease is an uncommon disease, accounting for only 0.18 to 1% of end-stage renal failure (2, 4), but it is responsible for 2.4 to 22% of the renal failure in children and adolescents in Europe and North America (7, 14, 15). Approximately 30 Japanese cases have been reported (16–19), one of which has neither a family history of renal disease nor typical symptoms and is assumed to be an atypical case (19). In Japan the actual incidence of this disease is still not known (20); there may be more such cases, especially isolated ones, than previously recognized. The screening conducted during school examinations includes urinalysis as a check for proteinuria and hematuria, but it seems insufficient for detecting nephronophthisis-medullary cystic disease. An earlier, more detailed form of screening, especially for children and adolescents, is needed for the early diagnosis of this disease. Measurement of the specific gravity of urine may prove useful, because a defect in the ability to concentrate urine is suggested to be the earliest demonstrable defect in renal dys-function (2).

We presented a case of nephronophthisis-medullary cystic disease in which there was no family history of renal disease, no typical symptoms and no growth retardation. When referred to our hospital, the patient presented end-stage renal failure. CT and ultrasonography showed medullary or cortico-medullary cysts in the kidneys. Measurement of the ability to concentrate urine and careful imaging evaluations of the kidney appear to offer the best hope for an early diagnosis. More detailed screening during school examinations is also needed for the early detection of this disease.

References

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