Case Report:

Nephronophthisis - medullary cystic disease

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Abstract:
Nephronophthisis (NPH) is a chronic tubulointerstitial nephritis with autosomal recessive inheritance that progresses to end-stage renal failure usually during adolescence. The first signs appear after 3 years of age with a urine concentration defect responsible for polyuria and polydipsia, failure to thrive and a progressive deterioration of renal function without signs of glomerular disease. Renal ultrasonography reveals normal-sized kidneys and at advanced stages, medullary cysts. Histologic lesions concern tubular basement membranes which are thickened and thinned. There is an associated interstitial fibrosis.

Introduction

Nephronophthisis (NPH) - Medullary Cystic Disease (MCD) complex, an autosomal recessive disorder initially described in 1945 by Smith and Graham and in 1951 by Fanconi. NPH is a chronic tubulointerstitial nephritis that uniformly progresses to end-stage renal disease (ESRD). With regard to the age of onset for ESRD, three clinical variants have been described: infantile, juvenile, and adolescent forms. Of these, juvenile NPH is the most common, which accounts for 5–10% of cases of ESRD in children.1,2 The disease has a characteristic renal histologic triad of tubular basement membrane disintegration, tubular atrophy with cyst development, and interstitial cell infiltration with fibrosis.3 Here we present a case of 18 year old male who presented with a disease that had a typical course of congenital chronic tubulointerstitial nephritis resembling that of NPH.

Case Report

A 18 year old boy presented with edema on legs and face, polyuria, polydipsia and hypertension for the last six months. He was not hospitalised in the past. He had mild mental retardation. His twin sibling died one month back with unexplained acute renal failure. There was no consanguinity of the parents in our case and no evidence of disease in any close relative. Investigations revealed a normocytic, normochromic anemia (Hb 6.5 g/dL). Urine analysis, culture and X-ray chest were normal. Acid base study revealed metabolic acidosis (pH = 7.192, BE = -20.5). Kidney function tests showed a blood urea of 83 mg/dL, S.Creatinine of 4.7 mg/dL with hypokalemia (2.7 mEq/L), hypocalcemia (6.9 mg/dL), normal serum
sodium (141 mEq/L) and serum uric acid of 4.7 mg/dL. Proteinuria ranged from 910-1670 mg/24 h and urine pH from 5.5. The highest urine specific gravity was 1010. Urinary sediment contained very few formed elements. Renal ultrasonographic Examination was normal. Renal ultrasonographic demonstrated increased echogenicity, normal kidney size and loss of corticomedullary differentiation. A renal biopsy had been performed a few weeks after admission and was sent to department of pathology. Microscopic examination showed the presence of cortical tissue that revealed variable atrophy of tubules with thickening of basement membrane and sclerosis of glomeruli. Interstitium showed loose fibrosis with thickening of blood vessels (Fig.1, 2). Special stains were also applied like periodic acid Schiff which showed PAS-positive basement membrane and Gomori methamine silver which confirmed the findings (Fig.3). Histology was suggestive of cortical atrophy. Immunofluorescence findings were non contributory. In view of family history possibility of nephronophthisis was likely. Conservative therapy and peritoneal dialysis was the on going treatment. Patient was advised genetic testing. Patient’s condition deteriorated and renal transplantation was advised.

Discussion

Juvenile NPH is an uncommon condition that affects girls and boys equally. The incidence is approximately 0.13 for 10,000 live births in Finland, whereas in Canada, it is 1 per 50,000 live births and in United States 9 per 8.3 million. The disorder has been reported worldwide. The first symptoms generally develop around 4–6 years of age. Polyuria and polydipsia related to a reduced urinary concentrating ability and loss of sodium conservation occurs early in the course of the disease, whereas glomerular filtration rate (GFR) remains normal. Decreased urinary concentrating defect is demonstrated by a low urinary osmolarity (<400 mosm/kg in the first urine sample in the morning), which does not increase after desmopressin acetate administration. Urinary sodium wasting may be responsible for hyponatremia and hypovolemia in cases of decreased sodium intake. Decreased growth velocity related to chronic dehydration and later to renal insufficiency results in growth retardation. Hematuria and proteinuria are absent or minimal. Blood pressure is normal before the onset of renal failure. Renal insufficiency is often present when the diagnosis is made. Late symptoms are related to the progressive renal insufficiency and include anemia, metabolic acidosis, nausea, anorexia, and weakness. ESRD develops at a mean age of about 13 years but can also occurs in some rare cases much later during adulthood. Renal ultrasound may be normal, with normal-sized kidneys, but renal parenchymal hyperechogenicity and loss of corticomedullary differentiation are often observed. At later stages, small cysts are present in the medulla. Renal biopsy shows severe tubular damage on light microscopy. Groups of atrophic tubules with thickened basement membranes alternate with groups of dilated or collapsed tubules. Homogeneous or multilayered thickening of tubular basement membranes is prominent, but disintegration of the basement membrane can also occur. Abrupt transition from one abnormality to another is highly suggestive of juvenile NPH. These various changes in the tubular basement membrane, although nonspecific, occur in NPH more extensively than in any kidney disorders with abnormal tubules. There is moderate to massive interstitial fibrosis with few inflammatory cells. The glomeruli are often normal, although secondary
sclerosis is observed in advanced disease.\textsuperscript{1} Extrarenal organ involvement in association with recessive NPH is exclusive to juvenile nephronophthisis. It can occur in combination with ocular motor apraxia type Cogan, with retinitis pigmentosa in Senior-Loken syndrome (SLS), with liver fibrosis and cone-shaped epiphyses in Mainzer-Saldino syndrome, and with coloboma of the optic nerve and cerebellar vermis aplasia in Joubert’s syndrome type B.\textsuperscript{6,7,8} There is extensive gene locus heterogeneity with at least three different loci for nephronophthisis by positional cloning the gene (NPHP1) for juvenile nephronophthisis (NPH1), as a first step towards understanding the pathogenesis of this disease group. Its gene product, nephrocystin, is a novel protein, which contains a src-homology 3 (SH3) domain. Twelve genes have been implicated in NPHP: NPHP1, NPHP2/INVS, NPHP3, NPH-P4, NPHP5/IQCB1, NPHP6/CEP290,NPHP7/GLIS2, NPHP8/RPGRIP1L, NP-HP9/NEK8, TMEM67, TTC21B, and XP-NPEP3.\textsuperscript{1,9,10}

**Conclusion**

In practical terms, NPHP must be considered among the differential diagnosis of any cause of renal failure of unknown origin. The diagnosis of NPHP can be based on the combined results of typical clinical history with polyuria, polydipsia and anemia; the classical appearance of the kidney on ultrasound and renal histology. The recognition that NPHP is part of a ciliopathy, with a wide clinical spectrum of disease will allow earlier diagnosis to be made, allowing for time for genetic counselling, appropriate genetic testing and improved treatment planning for ESRF. The appropriate diagnosis of NPHP is important not only for anticipating progressive renal failure but also for the implications on genetic counseling.

![Fig. 1-3 Photomicrograph showing variable atrophy of tubules with thickening of basement membrane and sclerosis of glomeruli. (H&E 100X, 200X, PAS 200X)](image)
References