Nephronophthisis

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Abstract

Nephronophthisis is a chronic tubulointerstitial nephritis with autosomal recessive inheritance that progress 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 multilayered or thinned. There is an associated interstitial fibrosis. Some children present with extrarenal symptoms. Nephronophthisis can be associated with tapetoretinal degeneration as in Senior-Loken syndrome (congenital nystagmus and early blindness). Other associations are possible: mental retardation, cerebellar ataxia, bone anomalies or liver involvement. A gene involved in the disease has been mapped to chromosome 2q13. Homozygous deletions in that region have been detected in 70% of affected children. This gene, NPHP1, encodes an internal protein, nephrocystin. Mutations in this gene are associated with 50 to 85% of cases. Genetic heterogeneity was demonstrated and a new gene, NPHP4 has been mapped on chromosome 1p36. This gene codes for nephrocystin-4. Mutations in the NPHP3 gene cause an adolescent form of Nephronophthisis, which may be associated with tapetoretinal degeneration or hepatic fibrosis. Mutations of the NPHP2 gene, which encodes for inversin are responsible for an infantile form of Nephronophthisis which progress to end stage renal failure before age 5.

Keywords

Cystic kidney disease, tubulointerstitial nephritis, renal failure, medullary cysts, *NPHP* genes

Disease name and synonyms

Nephronophthisis (NPHP)
Familial juvenile nephronophthisis (FJN)
Medullary cystic kidney disease, autosomal recessive.

Definition

FJN is an uncommon condition equally distributed in males and females. It almost always progresses to end-stage renal disease,

which typically develops before age 20 years [1,2]; most studies have found a mean age of about 13 years [3].

As in other genetic renal diseases (such as autosomal dominant polycystic kidney disease or hereditary nephritis), the rapidity of progression to renal failure is probably determined in part by the type and severity of the genetic defect. However, some data suggest that a similar clinical and histological phenotype occurs among kindred with clearly different genetic defects, including abnormalities in loci other than the nephrocystin gene [4].

Because no specific markers have been identified, the diagnosis is made by inference from the family history (if present), polyuria due to decreased concentrating ability, the relatively normal urinalysis, and the presence of a smooth renal outline and normal-sized or small kidneys on renal ultrasonography or intravenous urography(IVU). In addition, the latter tests often show multiple small and occasionally larger cysts at the corticomedullary junction [5,6]. Thin-section computed tomography (CT) is even more sensitive, detecting cysts as small as 5 mm in diameter [7].

Renal presentation of FJN is also relatively non-specific. The urinalysis is not helpful, generally revealing few cells or casts.

Prevalence

The incidence of the disease has been estimated to be 9/8.3 million live births in United States and 1/50.000 live births in Canada [8]. This disease is the most common genetic disease (around 15%) of patients progressing to renal failure.

Clinical manifestations

The clinical manifestations of FJN are caused by tubule injury leading to diminish urine-concentrating ability and sodium loss. These abnormalities precede any decline in the glomerular filtration rate and can also be demonstrated in asymptomatic siblings.

The first symptoms generally develop after the age of 1 year. They consist of polyuria with polydipsia and retarded growth. Volume balance is generally well maintained under normal sodium intake. However, hypovolemia, hyponatremia and elevation of the plasma creatinine concentration may ensue if sodium intake is diminished [1].

Urinalysis is not informative, generally revealing few cells or casts. Proteinuria may be a late finding reflecting the development of secondary glomerulosclerosis [1]. The tendency for sodium loss probably accounts for the typical absence of hypertension in this disorder.

Later findings are reflecting the progressive renal insufficiency: anemia, metabolic acidosis and early uremic symptom such as nausea, anorexia, and weakness. It has been estimated that FJN is responsible for approximately 2.4% of the cases of end-stage renal disease in children in the United States [9]. This percentage may be underestimated as studies from Europe have revealed a higher frequency of 15% [3].

Associated disorders

Other disorders in children and young adults that can present chronic renal failure and an uninformative urinalysis include chronic pyelonephritis, urinary tract obstruction and polycystic kidney disease. These disorders, however, are associated with diagnostic findings on IVU or renal ultrasonography-caliectasis with focal parenchymal scarring, hydronephrosis, and multiple bilateral cysts with enlarged kidneys, respectively. There is no dilatation of the urinary tract in FJN, but the bladder may be enlarged as a result of chronic polyuria.

The Senior-Loken syndrome, in which tapetoretinal degeneration accompanies FJN, is seen in 18% of cases and may result from a somewhat different genetic defect [10,11]. Leber's congenital amaurosis is the early-onset form; affected children are blind from birth, have flat electroretinograms, and develop retinitis pigmentosa. In the late-onset form, blindness occurs later during childhood. Other eye anomalies have been reported in association with FJN including coloboma, cataract, ambliopia, nystagmus and retinitis pigmentosa of an other origin.

Other organs may also be affected, although the mechanism by which these abnormalities occur is not understood:

- cerebral involvement, which is usually accompanied by retinal degeneration, can lead to mental retardation and cerebellar ataxia;
- bone anomalies can lead to cone-shaped epiphyses, which are always associated with other extrarenal manifestations [12].
- hepatic involvement may be characterized by hepatosplenomegaly and portal fibrosis with no or only mild bile-duct proliferation [13-15]

Treatment

There is no specific therapy for FJN other than correction of water and electrolyte imbalances that may occur. Dialysis followed by transplantation is the preferred approach for end-stage renal disease. The tubule injury does not recur in the transplanted kidney, which lacks the underlying abnormality.

Etiology

The gene for FJN without extrarenal symptoms has been localized to chromosome 2q13 between D2548 and D2551 [3,16]. Large homozygous deletions of approximately 250 kb in this region have been detected in 70% of the patients; such rearrangements can now be used for diagnosis, since this deletion has not been found in unaffected family members and more than 200 controls [4].

A gene for FJN was recently isolated by means of positional cloning [17,18]. The gene encodes for a protein, named nephrocystin, which has SRC (SRC is the symbol for the human gene homologous in sequence to the v-src gene of the Rous sarcoma virus) homology 3 and leucine-zipper domains, areas known to play roles in the interactions between proteins. The overall function of this protein remains unclear.

However, not all affected families appear to have defects in this gene [8,19,20]. In one study, for example, 6 out of 16 families did not show linkage to the locus 2q13, thereby indicating the existence of at least one additional genetic locus in this disorder [19]. Such suspect loci include chromosomal areas 6p21.1-p1.2 and 9q22-31 [9].

Genetic heterogeneity was demonstrated and a new gene, NPHP4 has been mapped on chromosome 1p36. This gene codes for nephrocystin-4. Mutations in the NPHP3 gene (locus 3q22) cause an adolescent form of Nephronophthisis, which may be associated with tapetoretinal degeneration or hepatic fibrosis. Mutations of the NPHP2 gene (locus 9q21-22), which encodes for inversin are responsible for an infantile form of Nephronophthisis which progress to end stage renal failure before age 5. [24-29]

Diagnostic methods

The kidneys in FJN show cysts of variable size that are irregularly distributed at the corticomedullary junction and in the medulla. Medullary cysts appear later during the course of the disease and are often absent in renal biopsies performed at an early stage [21,22]. Severe tubule damage is seen on light microscopy. Groups of atrophic tubules with thickened basement membranes alternate with groups of dilated or collapsed tubules [23]. The changes in the tubule basement membranes are highly suggestive of FJN: homogeneous or multilayered thickening of basement membranes is most prominent, although disintegration of the basement membranes can also occur. There is moderate interstitial fibrosis with few inflammatory cells. The glomeruli are often normal, but secondary segmental sclerosis is not uncommon in advanced disease.

Homozygous deletions of about 250 kb on chromosome 2p12 can be detected by the lack of polymerase chain reaction amplification of genomic DNA markers; this analysis provides a fast and accurate diagnosis of the disease in 70 percent of patients, thereby eliminating the need for a renal biopsy [3].

Antenatal diagnosis

Prenatal diagnosis can be performed only by direct genetic testing when a specific mutation or a deletion has already been identified in an affected sibling.

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