Ocular Manifestations of Hereditary Renal Disorders

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INTRODUCTION
There are many genitourinary disorders associated with ocular pathology. I shall discuss specifically the renal parenchymal disorders in which the mode of inheritance has been defined and will exclude disorders of the ureter, bladder, and urethra. Ophthalmologists are frequently asked to examine infants and children, since their findings may
offer supportive evidence for a specific diagnosis — for example, the finding of cystine crystals in the cornea in cystinosis. Also, they may prevent ocular handicaps. Hereditary renal parenchymal diseases may also be considered as structural defects (such as cystic renal disease) and tubular transport defects (as in cystinosis and Lowe’s syndrome), glomerulopathies (as in Alport’s syndrome), and enzymatic deficiency (as in Fabry’s disease).

**ALPORT’S SYNDROME**

Alport’s syndrome, the most common of all hereditary renal disorders, has the clinical features of hematuria, proteinuria, and progressive azotemia. In addition, there may be sensorineural deafness. The earliest and most common manifestation is hematuria, which may occur in infancy. The male usually has progressive renal insufficiency, which occurs in the second decade, while the female may have hematuria without progressive renal insufficiency (although this is not universal, and indeed women have succumbed to end-stage renal disease). Analysis of several pedigrees has led to the conclusion that the inheritance is of an autosomal dominant defect, most likely with nonrandom chromosome segregation and preference association of gene-bearing autosomal with the X chromosome.

The renal pathologic findings at postmortem examination are chronic glomerulonephritis and pyelonephritis. The electron microscope has recently aided our understanding, and before the onset of renal insufficiency there is splitting of the basement membrane. More observations are needed to verify these recent reports as being diagnostic.

Ocular defects occur in 10 per cent of the patients and include cataracts, microspherophakia, anterior lenticulons, myopia, and nystagmus, which have been described in families and may represent additional facets of the defective gene. Deafness may not be clinically apparent, but audiometry often demonstrates the earliest finding of high-frequency loss. This may be demonstrated in half of the patients. This, too, may worsen as the patient ages. There is no specific treatment that will arrest the renal disease, and these patients ultimately require hemodialysis and renal transplantation for survival.

**MEDULLARY CYSTIC DISEASE**

Medullary cystic disease and familial juvenile nephronophthisis are pathologically indistinguishable. The former has its onset in early adulthood, with progression to azotemia within five to 10 years; the inheritance is autosomal dominant. Juvenile nephronophthisis usually has its onset in the first decade, and autosomal recessive inheritance and consanguinity have been found. The ultimate outcome is chronic renal disease during the second decade. The earliest manifestations are anemia, failure to thrive, hypothenuria, and salt-losing nephropathy. While in young adults there may be nonspecific complaints of easy fatigue, lethargy, and anorexia and evaluation reveals uremia, the diagnosis is frequently difficult to make because intravenous pyelogram usually shows poor concentration and rarely demonstrates the cysts. Open renal biopsies are sometimes required in order to obtain adequate tissue. Microscopically, one finds interstitial fibrosis and-

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* Microspherophakia: Abnormality of the lens, which is small and round.
** Lenticulons: Rare abnormality of the lens characterized by conical prominence of the anteroposterior lens surface.
sociated periglomerular fibrosis as well as cysts in the corticomedullary area.

The frequency of the ocular component in medullary cystic nephronophthisis is not known, but it is characterized by pigmentary retinal dysplasia (retinitis pigmentosa) (Figure 1), with progression leading to blindness. This, too, is a progressive disorder requiring hemodialysis and transplantation for survival.

**LOWE'S SYNDROME**

The oculocerebrorenal syndrome (Lowe's syndrome) is a congenital hereditary disorder limited to males. It is characterized by mental retardation, hypotonia, glaucoma, organic aciduria, aminoaciduria, proteinuria, and diminished renal function. The appearance is rather typical, with a chubby habitus, pale skin, prominent frontal bossing, inattentiveness, hyperexcitability, and, during waking hours, emission of a high-pitched scream and repetitive movements of the extremities. The eyes are commonly large with megalocornea and other signs of corneal clouding. Some children may have normal-size eyes or microphthalmus. Cataracts are either nuclear or in the posterior lens (Figure 2), dense, and essentially opaque. They are bilateral and are present at birth in almost all cases. Typically, there is a searching nystagmus with random oscillation and periodic movements. Glaucoma is present in most cases, and it may appear at different ages. Postmortem examinations of the eyes have revealed cataracts, with congenital anomalies in the cornea, ciliary body and processes, macula, and ora serrata. The optic nerve, anterior chamber, and canal are normal. At one year of age, it is possible to detect clinical signs of rickets. The joints are characteristically hypermobile, with poor muscle tone. Deep tendon reflexes are usually completely absent; if present, they are weak and difficult to elicit.

Laboratory findings are typical, usually with reduction of carbon dioxide content and concomitant hyperchloremia. Blood amino acids
are normal. Serum calcium is normal. Phosphate is significantly decreased, with elevation of alkaline phosphatase typical of rickets. Proteinuria is always present. Glycosuria may be present, and amino acids are constantly present and abnormally increased in amount. In addition, organic aciduria is present. The renal clearances are quite variable, usually normal at birth and progressively decreased with age. Patients at early ages exhibit no renal pathology despite the metabolic derangements. Later there are diffuse tubular changes with little or no glomerular involvement and dilatation of tubules, which may contain proteinaceous casts. At five or six years of age, there is focal involvement with glomerular fibrosis and hyalination; tubular atrophy is present.

The disease appears in males. One report described two families with females with the disease. Typical pedigree analyses indicated that the disease is carried through the maternal line. Transmission appears X-linked. Detection of the carrier state is not uniform. An inconsistent finding has been a punctate opacity in the lens of the mother.

The natural history of the disease is such that patients die of either severe renal insufficiency with dehydration or intercurrent infection. Only a few patients have lived beyond adolescence. The course of this disease consists of three distinct periods. In the neonate the only clinical findings are cataracts and glaucoma. The second phase is the presence of the hypotonia, early manifestation of metabolic acidosis, and subsequent development of rickets. The third phase is progression to chronic renal insufficiency if the patient lives beyond the first decade. No specific treatment has been demonstrated to be effective in arresting progression.

**FABRY'S DISEASE**

The hallmark of Fabry's disease is the characteristic dermatologic findings, which usually become manifest at puberty. The initial findings are macules and papules; these are typically found in the umbilicus, but angiokeratomas may also be found on the trunk and extremities. Subsequently there is acral pain, paresthesias, febrile episodes, vasomotor instability, and anhidrosis. This is inherited as an X-linked trait with complete penetrance in males. Female patients are usually asymptomatic. Occasionally, they may have the full-blown manifestations of the disease, or they may have only corneal opacities. The ocular manifestations include aneurysmal dilatation, tortuosity of the conjunctiva and retinal vessels, and corneal opacities. The opacities may be diffuse haziness or whorled streaks in...
the corneal epithelium (Figure 3). The renal manifestations early in the course of the disease are characterized by hematuria and a birefringent "Maltese cross," which appears in the urinary sediment. The latter is a lipid inclusion. In addition, one finds proteinuria and casts and subsequent gradual deterioration of renal function and uremia by the third or fourth decade. The pathogenesis of this entity is the systemic accumulation of a glycolipid, trihexosyl ceramide, particularly in the cardiovascular and renal systems. This is most obvious in the endothelial and epithelial cells of the glomerulus, as well as in vessels throughout the body. The diagnosis is made biochemically by finding increased levels of trihexosyl ceramide in urine and plasma and deficient activity of ceramide trihexosidase in cultured fibroblasts. Specific treatment is purely experimental — first, with replacement of the deficient enzyme; second, by genetic counseling; and, third, with management of the chronic renal disease by hemodialysis and renal transplantation. It is interesting to note that the transplanted kidney does not progressively develop chronic renal disease secondary to accumulation of the lipid.

**CYSTINOSIS**

Cystinosis is a rare, recessive inherited disease associated with deposition of L-cystine crystals in the eye, the reticuloendothelial system, the kidney, and many other organs. It is characterized by a high content of free cystine intracellularly. Children with this disorder appear normal at birth; by six to nine months of age, however, they have symptoms of renal Fanconi's syndrome, which is characterized by polyuria, polydipsia, glycosuria, aminoaciduria, and phosphaturia. The children remain short and exhibit failure to thrive with progressive glomerular insufficiency; end-stage kidney disease develops by 10 years of age. The specific metabolic defect that leads to the accumulation of cystine remains unknown. Cystine crystals are not present at birth in children with cys-
tinosis but are seen in bone marrow aspirates and lymph node biopsies at four to five months of age.

Postmortem studies of eyes from children with cystinosis demonstrate more extensive changes than those observed in the fetus. There is degeneration of the pigmented epithelium, with loss of cell borders and scattering of pigmented granules. The vacuolization of the retinal pigmented epithelium may represent various recognizable histologic abnormalities other than cystinosis, but this is also found in the fetus. The earliest ophthalmologic change is a retinopathy, which has been described in a five-week-old child; slit-lamp examination did not demonstrate refractile bodies in the conjunctiva, cornea, or sclerae (Figure 4). The earliest pigmentary change is an irregular distribution of fine granular pigmentation of the retina.

Examination of these patients includes evaluation of urine amino acids and bone marrow in a search for the characteristic hexagonal crystals, which may be seen as early as 10 weeks. Funduscopic examination as well as slit-lamp examination should be done. The finding of glycosuria or phosphaturia is noted. Rickets is usually present by one year of age. Treatment is symptomatic with progression to chronic renal insufficiency, usually by the end of the first decade. Renal transplantation has been successfully performed; although the cystine crystals are found in the transplanted kidney, progression does not appear to occur. Too few of these patients have been observed for us to establish the course of the visual disturbance. Prenatal diagnosis is now possible with amniocentesis where the nonprotein cystine in cultured amniotic fluid cells is increased. Fetal autopsy at 18 weeks of age has demonstrated the vacuolization of pigmented material.

**SUMMARY**

Our metabolic understanding of these entities is quite limited and awaits continued basic research for many of the answers. In the meantime, the greatest service we can render to our patients is early recognition of these entities by the primary physician and specialist so that subsequent genetic counseling can be provided.

**BIBLIOGRAPHY**