Cystic and Inherited Kidney Diseases
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AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Epidemiology

- The most common renal hereditary disease, affects 1 in 400 to 1,000 live births.\(^1\)
- Affects all races with equal frequency.\(^1\)
- Accounts for 5% of the end-stage renal disease (ESRD) population in the United States and in Europe.\(^2\)

Inheritance

- Mutations in the polycystic kidney disease (PKD)1 gene account for approximately 85% of affected families.\(^3\)
- The PKD1 gene is located on the short arm of chromosome 16 (16p.3.3).
  - PKD1 codes for a 4,304-amino-acid protein (polycystin 1)\(^2\) with as yet undefined function but interacts with polycystin 2 and is involved in cell cycle regulation and intracellular calcium transport. Polycystin 1 localizes in the primary cilia of renal epithelial cells.\(^4\)
- Primary cilia function as mechanosensors where a calcium current is created by bending the cilium by luminal flow.\(^4\)
- Mutations in the PKD2 gene account for 15% of affected families.\(^3\)
  - The PKD2 gene is located on chromosome 4 (4q.21.2).\(^2\)
  - PKD2 codes for a 968-amino-acid protein (polycystin 2) structurally similar to polycystin 1 and is a member of the family of voltage-activated calcium channels.\(^2\)
  - Polycystin 2 interacts with polycystin 1 and colocalizes to the primary cilia of renal epithelial cells.\(^4\)
- Few families are not linked to chromosome 16 nor 4. A third locus for ADPKD has been sought but not yet identified, suggesting only 2 genes are responsible for the disease.\(^5\)
- PKD1 and PKD2 mutations have different prognostic implications, with PKD2 patients developing renal cysts, hypertension (HTN), and ESRD at a later age than PKD1 patients.\(^3\)
- A genotype to phenotype correlation has not yet been established in PKD1 and PKD2 individuals.
  - The second-hit theory suggests that cyst formation is focal, affecting <5% of the nephron population, and is related to a second somatic mutation in the remaining wild-type allele.\(^6\)
- Variability in disease severity within families and clustering of extrarenal manifestations of the disease suggest that environmental factors and modifier genes are involved in the clinical severity of ADPKD.

Pathology of the Renal Disease

- Characterized by massive enlargement of the kidneys secondary to cyst growth and development.
- Epithelial lined cysts arise from a small population of renal tubules (<5% of the nephrons) and ultimately detach from the parent nephron (usually when >2 cm in diameter).\(^7,8\)
- Benign adenomas are present in 25% of ADPKD kidneys.
- Significant interstitial fibrosis is present once ESRD is reached.
- Profibrotic and mitogenic factors (transforming growth factor \(\alpha\), angiotensin II, endothelial growth factor, endothelin) have been found in cystic epithelia and cyst fluid.
Diagnosis

Radiologic

● Those deciding to undergo a diagnostic workup for the presence of ADPKD require pretest and posttest genetic counseling.
● Radiological imaging is required. Ultrasound is the current imaging modality of choice in at-risk individuals (positive family history in a parent).
● The presence of multiple bilateral cysts is required for a diagnosis (Ravine criteria), see Table 1.
● These age-specific data have been developed in reference to PKD1 patients. Reliable information is not yet available for PKD2 individuals.
● Renal enlargement in addition to the presence of cysts is a universal feature of ADPKD.
● A normal ultrasound with increasing age has a higher negative predictive value (negative ultrasound at age 20 infers <10% chance of inheritance).
● When greater certainty is needed to determine affection status (eg, living related donor for kidney transplantation), computed tomography or magnetic resonance imaging may be more informative or genetic testing may be required.

Genetic

● Gene linkage analysis can be performed if DNA from >3 affected family members is available.
● Mutation screening is commercially available to determine if mutations are present in the PKD1 or PKD2 genes.
● Direct sequencing is the most accurate and reliable method to screen for the presence of PKD1 or PKD2, but expense is a limiting factor.
● Denaturing high-performance liquid chromatography has been used to identify mutations in PKD1 and PKD2 individuals with 75% and 95% success rates, respectively.

Clinical Manifestations

Renal

● Decrease in renal concentrating ability is an early manifestation.
● Dipstick-detected proteinuria occurs in <18% with most demonstrating <1 g/24 h.
● Microalbuminuria is more common than proteinuria, occurring in 35% of ADPKD individuals.
● Chronic pain: In the majority of patients, may require narcotics.
● Hypertension (HTN).
  ■ Common and early, occurring in about 60% of patients with normal renal function.
  ■ Mean age of onset is 31 years of age, with men demonstrating greater blood pressure levels than women.
  ■ Occurs with increased frequency in children with ADPKD (10% to 15%).
  ■ Activation of the renin angiotensin system occurs secondary to intrarenal ischemia from cyst expansion.
  ■ Contributes to a more rapid loss of renal function.
  ■ Recommended blood pressure levels are not evidence based but consistent with current recommendations for those with nonproteinuric renal disease (<130/80 mm Hg). Important considerations for the appropriate antihypertensive agents to be used are based on indirect evidence that inhibition of the renin-angiotensin aldosterone system with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker may prevent progression of renal disease.
  ■ Rigorous blood pressure control and ACE inhibitor use are more effective in reversing left ventricular hypertrophy compared with dihydropyridine calcium channel blockers in ADPKD patients.
  ■ ACE inhibitors are more effective in reducing proteinuria in ADPKD patients as compared with other antihypertensive agents.
Hematuria.
- May be secondary to cyst hemorrhage, cystitis, pyelonephritis, nephrolithiasis.\(^1\)
- For cyst hemorrhage, analgesia, bed rest, and hydration shorten the duration of hemorrhage.
- Nephrolithiasis affects up to 20% of patients.
- Calcium oxalate or urate stones are the most common.
- Hypocitraturia occurs in 2 out of 3 patients with ADPKD and nephrolithiasis.
- Structural deformations secondary to renal cysts contribute to stone formation.\(^1\)

Cyst infection.
- Treatment requires antibiotics that can penetrate the cyst (trimethoprim-sulfamethoxazole, ciprofloxacin, chloramphenicol, vancomycin).
- Duration of therapy is longer than for uncomplicated cystitis or pyelonephritis and may require up to 4 weeks of intravenous antibiotics.\(^18\)
- Blood cultures yield identification of the infecting organism more often than urine cultures.
- Computed tomography and magnetic resonance imaging may demonstrate complicated cysts in the area of pain or symptoms.\(^1\)\(^19\)

Renal failure.
- Rate of progression to ESRD is variable between patients with ADPKD.
- Once renal insufficiency is reached, progression to renal failure is universal.
- Average rate of decline of renal function in those with renal insufficiency is 4.0 to 5.0 mL/min/\(y\).
- Negative prognostic factors for progression to renal failure are male sex, the presence and early onset of HTN, increased renal size, and increased urinary albumin excretion.
- Dialysis: Better survival than the general dialysis population.
- Cardiovascular and cerebrovascular causes are the most common causes of death.
- Transplantation: Better patient survival than in other renal disease populations. There is no need to remove the kidneys prior to transplantation unless there are ongoing clinical complications like cyst infections.\(^1\)\(^2\)

Extrarenal
- Hepatic cysts.
  - Most common extrarenal manifestation.\(^2\)
  - Isolated autosomal dominant polycystic liver disease (ADPLD) has been reported and the gene responsible is on chromosome 19.\(^20\)
  - Liver cysts present approximately 10 years after renal cysts.
  - Severe hepatic disease predominantly affects women.
  - Liver function is preserved even with massive polycystic liver disease.
  - Biochemical abnormalities are few and include a mild increase in serum alkaline phosphatase.
  - Hepatic enlargement is the predominant complication of PKD. This results in symptoms of shortness of breath, pain, decreased mobility, ankle swelling, and (rarely) inferior vena cava compression. Rarely patients require surgical cyst deroofing, resection, or transplantation.\(^2\)

Intracranial aneurysms (ICAs).
- Occur in 4% to 8% of asymptomatic ADPKD patients.
- ICAs cluster in small numbers of families (<5% of all ADPKD families) with multiple affected members.
- Occur mostly in the anterior circulation.
- Rupture of ICAs is associated with >50% immediate mortality and >80% permanent morbidity.
- Screening is indicated in asymptomatic patients with positive family history for ICA, personal history of subarachnoid hemorrhage, or high-risk occupation (eg, airline pilots, scuba divers), or prior to major elective surgery that may affect intracranial hemodynamics.
- Imaging modality of choice for screening is a time-of-flight 3-dimensional magnetic resonance arteriogram.
- No consensus on the management of small asymptomatic aneurysms (<10 mm),
but observation and follow-up imaging are suggested.

- Elective surgical management recommended for asymptomatic aneurysms >10 mm.2,21
- Other vascular abnormalities include dolichoectasia and intracoronary aneurysms. Abdominal aortic aneurysms do not occur with increased frequency in ADPKD.2
- Cardiac disease.
  - Mitral and aortic prolapse and regurgitation.
  - Valvular disease is caused by loss of collagen and myxomatous degeneration.
  - Prophylaxis for bacterial endocarditis required in the presence of regurgitation.2
- Diverticular disease.
  - Increased prevalence and rate of complication related to diverticular disease in patients with ESRD from ADPKD.
  - Diverticulitis and colonic perforation are 2 serious complications that require immediate attention. Management is similar to that in non-ADPKD patients.2
  - In non-ESRD patients with ADPKD, there is no increased prevalence of diverticular disease compared with the general population.22
- Hernias.
  - There is an increased incidence of abdominal and inguinal hernias (up to 45% of ADPKD patients).23
  - Careful assessment of these patients before initiating peritoneal dialysis is required to identify small ventral hernias.

ADPKD in Children

- Some patients have early onset of the disease (in utero or in the first year of life).
- The reason for the early onset is unknown. Mutation type does not correlate, however, a contiguous gene deletion of the PKD1 and tuberous sclerosis complex (TSC) 2 gene has been found in some early-onset individuals.24
- Siblings of these children are at increased risk of early disease.25
- Renal involvement is similar to that in adults. Distinguishing ADPKD from autosomal recessive PKD (ARPKD) may be difficult. Ultrasonographic assessment of the parents is needed. The presence of pancreatic or hepatic cysts favors the diagnosis of ADPKD. Congenital hepatic fibrosis is uniformly present in ARPKD and most often is the key to a correct diagnosis.
- In affected individuals renal cysts are present with increasing frequency with age. More than 90% of affected individuals will demonstrate cystic abnormalities by 20 years of age.
- A single cyst in both kidneys is adequate to make a diagnosis of ADPKD in an at-risk child.9
- HTN is common in ADPKD children, occurring in 10% to 15% of individuals.
- Cerebral malformations (ICAs) have rarely been described in ADPKD children.2

ADPKD and Pregnancy

- The fertility rate is similar in ADPKD men and women as compared with that of the general population.26
- Increased frequency of ectopic pregnancies.
- Blockade of the seminiferous tubules resulting in male infertility has been reported in ADPKD.
- Pregnancy outcomes are similar to those in the general population in normotensive ADPKD women with normal renal function.
- Hypertensive ADPKD women are at increased risk of preeclampsia and fetal loss.
- Women with renal insufficiency have similar potential complications as those with other chronic renal diseases.1,2

Genetic Counseling

- Genetic counseling is recommended pretesting and posttesting for those individuals at risk for ADPKD who are planning to undergo diagnostic testing.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPKD)

Epidemiology

- Affects 1/10,000 to 1/40,000 individuals.27
Inheritance
● Autosomal recessive disorder, with at-risk offspring having a 25% chance of inheritance.
● Mutations in a single gene on the short arm of chromosome 6p 21.1.27
● Gene has been identified and sequenced.28,29

Pathology
● The protein encoded by the PKHD1 gene is called polyductin or fibrocystin. It is composed of 4,074 amino acids and is characterized by a single transmembrane segment and a short cytoplasmic C-terminal.30
● There is also evidence that abnormalities of the primary cilia play a role in the development of ARPKD.30
● Renal cysts or ectatic dilatation from the distal collecting ducts.
● Congenital hepatic fibrosis is a universal feature.
● Spectrum of disease: Mild kidney disease and severe liver involvement or vice versa.31

Diagnosis and Clinical Manifestations
● Prenatally: Oligohydramnios, enlarged kidneys, and lung hypoplasia with resultant Potter facies.32
● Infancy: Pneumomediastinum, pneumothorax, HTN, cardiac hypertrophy, endomyocardiofibrotic congestive heart failure, and renal failure.
● Older children: Hepatic fibrosis, portal HTN, and complications of variceal bleeding, thrombocytopenia, and anemia predominate.
● Infants with severe renal disease have a high perinatal mortality.
● Infants who survive the first year have a 50% to 80% chance to reach age 15.

Therapy and Prognosis
● Perinatal period: Prognosis depends on pulmonary status secondary to increased abdominal girth from bilateral renomegaly and pulmonary hypoplasia.
● HTN: Should be treated with salt restriction and ACE inhibitors. Target blood pressure should be below the 75th percentile for age and sex of the child.
● Renal insufficiency.
  ■ No kidney enlargement occurs with progression of disease unlike ADPKD.
  ■ Variable course of progression with 2 separate populations based on level of severity of renal dysfunction at the time of birth. Appropriate anemia and growth management should be addressed for all ARPKD children with renal insufficiency.
  ■ All ARPKD children are candidates for dialysis and transplantation.
● Hepatic insufficiency.
  ■ Hepatocellular damage or liver synthetic dysfunction is rare.
  ■ Portal HTN usually starts between ages 5 and 10 years.
  ■ Portosystemic shunts used for severe varices.
  ■ Candidates for liver transplantation or combined liver/renal transplantation.

ALPORT’S SYNDROME OR HEREDITARY NEPHRITIS

Genetics
● Prevalence of genetic mutation estimated at 1 in 5,000 to 1 in 10,000.
● Accounts for 1% to 2% of ESRD cases.
● X-linked inheritance in almost all cases (85%).
● Carrier mothers may have hematuria secondary to lyonization (random inactivation of one of the X chromosomes).
● Of the non–X-linked cases, most are autosomal recessive.33

Pathogenesis
● Type IV collagens are essential constituents of basement membranes. Six α chains of collagen IV (COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6) assemble into 3 sets of triple helical molecules called protomers. These in turn unite to form collagenous networks.34
● Each α chain has 3 domains: a short 7S domain at the N-terminal, a collagenous domain, and a noncollagenous domain at the C-terminal.34
● The α1 and α2 chains are found in all basement membranes.
● The α3.α4.α5 protomer is expressed in the glomerular basement membrane (GBM), some renal tubular membrane, the lung, testis, cochlea, and eye.34
● The α3.α5.α6 protomer is found in the skin, smooth muscle, esophagus, and Bowman’s capsule.34
● In the X-linked form, the primary abnormality is in the noncollagenous domain of type IV collagen, and involves the gene coding for the α5 chain (COL4A5).33
● In the autosomal recessive form, the abnormality involves either the α3 or the α4 chain of type IV collagen. Both genes responsible for these proteins are on chromosome 2.33
● Gene mutation appears to result in a post-translational defect that prevents protomer assembly.34

Renal Manifestations
● Hematuria is the characteristic clinical feature of Alport’s syndrome. Microscopic hematuria is detected in all males and 95% of females carrying the X-linked defect. All patients homozygotes for the recessive trait have microscopic hematuria as well.33
● Recurrent episodes of gross hematuria occur in 60% to 70% of hemizygotes, sometimes in association with symptoms of upper respiratory tract infection, most often before age 15. Gross hematuria can also be observed in one third of female carriers of the X-linked mutation.
● Proteinuria, initially absent, usually appears after a few years of life in all hemizygotes and autosomal recessive homozygotes and may reach the nephrotic range.35
● With time, proteinuria worsens, renal insufficiency develops, and HTN ensues. The risk of progression to ESRD is highest among hemizygotes and autosomal recessive homozygotes.33
● Variability in clinical course is related to the type of genetic mutation. Genotype-phenotype relationships exist: Among hemizygotes, the likelihood of ESRD before the age of 30 (the so-called juvenile type) is significantly higher in individuals with large rearrangement of the COL4A5 gene or with a mutation leading to a stop codon, than in those with splice-site or missense mutation.33,36

Extrarenal Manifestations
● Sensorineural hearing loss.
  ■ The most common extrarenal manifestation.
  ■ The deficit is never congenital and can be initially uncovered by audiometry.
  ■ It progresses to complete hearing loss at variable rates depending on the genetic mutation.
  ■ The cochlea is the site implicated.33,37
● Ocular defects.
  ■ Anterior lenticonus, ie, forward protrusion of the anterior surface of the lens caused by weakening of the type IV collagen in the anterior lens capsule, is pathognomonic of the disease.
  ■ Retinal flecks, ie, small yellow or white dots around the macula, are the most common findings. Corneal dystrophy has been reported as well.37
● Leiomyomatosis of the esophagus and genitalia.
  ■ Manifestation is rare.
  ■ Results from deletion of the 5’ end of the α5 and α6 genes.
  ■ Female carriers of the defect exhibit diffuse leiomyomatosis.33

Diagnosis
● Suspected in a patient with hematuria with or without hearing loss and a positive family history.
● Confirmation requires a renal biopsy.
  ■ The characteristic histologic feature is variable thickness of the GBM with lamellation of the lamina densa by electron microscopy.
  ■ The co-absence of α3, α4, and α5 chains on staining is highly specific for Alport’s syndrome.33,35
● The α5 and α6 chains of collagen type IV but not the α3 or α4 chains are expressed in the epidermal basement membrane, so biopsy of the skin can distinguish the X-linked from the autosomal recessive form: the absence of α5 chain from the epidermal basement membrane is highly
specific for the X-linked Alport’s syndrome.33

● Molecular diagnosis can be done in patients whose family has a characterized genetic mutation.33

**Treatment**

● There is no specific treatment.

● Aggressive treatment of HTN and protein restriction are warranted.

● As in other proteinuric diseases, the use of ACE inhibitors is advocated.38

● Cyclosporine use is controversial, but may slow the progression of renal disease in patients with aggressive nephropathy.39

● Dialysis support is needed for ESRD.

● Transplantation can be performed.

  ■ Patients develop alloantibodies to the Goodpasture antigen (in the α3 chain of the type IV collagen) because of lack of recognition of the antigen that was absent in the native kidney.

  ■ However, <10% of patients develop post-transplant anti-GBM disease. Treatment is similar to that of primary anti-GBM disease. Graft loss in these cases is common, with a high rate of recurrence after another transplantation.35,40

**THIN BASEMENT MEMBRANE DISEASE (TBMD)**

● Inherited renal disease of the GBM clinically characterized by persistent microscopic hematuria.37

● Unlike Alport’s syndrome, it is inherited in an autosomal dominant fashion, is not accompanied by extrarenal manifestations, and has a benign course.37

● The diagnosis is established by renal biopsy if needed.

● Pathologically characterized by unremarkable light microscopy and immunofluorescence studies. On electron microscopy, there is diffuse thinning of the GBM usually defined as a thickness of <250 nm for adults and <200 to 250 nm for children.35

● A recent study suggests an abnormality in the α5 chain of collagen IV as the underlying reason for the TBMD.41

**FECHTNER AND EPSTEIN’S SYNDROMES**

● Both syndromes are characterized by progressive nephropathy, sensorineural hearing loss, cataracts, and macrothrombocytopenia. The presence of Dohle-like bodies in leukocytes differentiates Fechtner from Epstein’s syndrome.42

● Both disorders are inherited in an autosomal dominant fashion.37

● Despite the common clinical features they share with Alport’s syndrome, both Fechtner and Epstein’s syndromes were found to be genetically distinct. They result from mutations in MYH9, the gene encoding nonmuscle myosin heavy chain 9 located on chromosome 22.37

● Recent evidence suggests that the MYH9 mutations alone cannot account for the renal anomalies. Predisposing factors or modifier genes may be needed for the development of nephropathy.42

**TUBEROUS SCLEROSIS COMPLEX (TSC)**

**Genetics**

● Tuberous sclerosis affects 40,000 Americans and approximately 2 million people worldwide.43

● It has an autosomal dominant pattern of inheritance, with a high rate of spontaneous mutations (65% to 75% of patients).44

● There are 2 genes causing the tuberous sclerosis clinical phenotype:

  ■ TSC1 is found on the long arm of chromosome 9 (9q34), its protein product is called Hamartin.

  ■ TSC2 is found on the short arm of chromosome 16 (16p13.3). Its protein product is named Tuberin. The gene is located only 48 base pairs of DNA from the gene for adult-onset PKD (PKD1). Most (75%) of sporadic cases result from mutations in the TSC2 gene.44

● Both tuberous sclerosis genes are tumor-suppressor genes.24

● Both protein products (Hamartin and Tuberin) colocalize in pathologic lesions of TSC patients and interact together. The nature of this interaction is unknown still.44
Many of the tumors in TSC show a loss of heterozygosity for TSC1 or TSC2 genes, suggesting that 1 mutation is acquired embryonically and another is acquired later on somatically (2-hit hypothesis). Mosaicism in TSC has been described:

- Somatic mosaicism: The mutation is not found in all cell lines.
- Germ-line mosaicism: The mutation is found only in gonadal cells, and is therefore transmitted to offspring while parents are spared from any disease manifestation.

A severe phenotype called very early onset PKD has been described and results from contiguous deletion of both TSC2 and PKD1 genes.

Clinical Manifestations

Renal

- Five different lesions can occur:
  - Benign angiomyolipomas are the most common (70% to 80% of adults), their diagnosis is highly dependent on the determination of their fat content by computed tomography or magnetic resonance imaging. The major complication from these lesions is bleeding, the risk of which increases once their size is >4 cm.
  - Cysts are the next most common (20% of patients), these are multiple and bilateral.
  - Malignant angiomyolipomas.
  - Oncocytomas.
  - Renal cell carcinomas.

Skin and eyes

- A multitude of lesions used for diagnostic purposes, most important are facial angiofibromas, ungual or periungual fibromas, shagreen patches, and hypomelanotic macules.
- Retinal hamartomas are most common ocular manifestations.

Central nervous system

- Epilepsy.
  - The major neurologic manifestation, affecting 85% of patients.
  - Seizures usually begin at few months of age as infantile spasm, carry a poor prognosis (cognitive impairment), and usually progress to other types of seizures.

- Intractable seizures.
  - For these patients, surgery is an option (either removal of a focal lesion or corpus callosotomy).
- Cortical tubers and subependymal nodules.
- Giant cell astrocytomas.
  - Occur in 5% of patients.
  - Are usually localized close to the foramen of Monroe and can give rise to increased intracranial pressure.

Cardiac

- Cardiac rhabdomyoma.
  - A rare manifestation.
  - Can be detected in utero by ultrasound as a cardiac mass.

Pulmonary

- Lymphangioleiomyomatosis.
  - Is a progressive lung disease seen almost exclusively in female patients of reproductive age.
  - Affects 1% of individuals with TSC.
- Multifocal micronodular pneumocyte hyperplasia (MMPH).
  - Affects men and women.
  - May accompany lymphangioleiomyomatosis.

Diagnostic Criteria

In July 1998, the National Institutes of Health sponsored a consensus conference of international experts to review the literature on TSC, and to come up with diagnostic criteria (summarized in Table 2).

Anderson-Fabry Disease (AFD)

Genetics

- It is an inborn error of glycosphingolipid metabolism caused by a deficiency of the lysosomal hydrolase α-galactosidase A (α-Gal A).
- It is an X-linked lysosomal storage disease, the α-Gal A protein is encoded by a gene mapped to the long arm of chromosome X (Xq22.1).
- The gene is mapped to 7 exons. Mutations have been described in every exon: 57% are
missense mutations, 11% nonsense, 18% partial gene deletions, 6% insertions, and 6% RNA processing defects caused by abnormal processing.

The disease manifests primarily in hemizygous males and to some extent in heterozygous females (carriers).

Estimated frequency of 1 in 117,000 male live births.

Median survival is 50 years for affected males and 70 years for carrier females.  

Pathogenesis

Glycosphingolipids are components of plasma membrane that are normally degraded in the lysosome. Deficient activity of α-Gal A activity leads to accumulation of these glycosphingolipids with terminal α-galactosyl residues derived mostly from the turnover of cells in the kidneys, liver, lungs, and erythrocytes.

The genotype/phenotype correlation has not been established yet.

Diagnosis of Fabry’s disease can be made by measurement of plasma or leukocyte α-GAL A activity, skin biopsy, examination of urine sediment, or sequencing of the defective gene.  

Clinical Manifestations

Renal

Urinary concentrating defect is the earliest manifestation.  

Proteinuria usually in the subnephrotic range develops in teenagers. In patients that develop nephritic-range proteinuria, the occurrence of full blown nephritic syndrome remains rare.  

Clinical nephropathy develops at a mean age of 27 years.  

HTN is not a common feature of the disease.  

There is a clear correlation between the level of residual enzyme activity and the severity of renal involvement, with chronic renal insufficiency being worse with lower levels of enzymes activity; this clinically corresponded to a younger age of onset of renal dysfunction.  

Histologically, the kidney reveals deposition of glycolipids in glomerular cells (mostly podocytes but also mesangial and endothelial cells), tubular epithelial cells, and vascular cells. Renal dysfunction is paralleled by segmental and ultimately global sclerosis, tubular atrophy, and interstitial scarring.  

Electron microscopy demonstrates enlarged lysosomes full of lamellar membrane structures.  

Urine sediment shows tubular cells with typical inclusions seen by light and electron microscopy.  

Patients with proteinuria or chronic renal insufficiency should have aggressive blood pressure control, and should be treated with ACE inhibitors based on a theoretical benefit from these agents.
The use of recombinant α-Gal A in clinical trials for 6 months showed improvement in glomerular architecture, and reduced glycolipid deposition in the kidney and even showed improvement in glomerular filtration rate.46,48

AFD is a rare cause of ESRD. Hemodialysis is the more likely modality of renal replacement treatment. At 3 years survival for Fabry’s patients was 63% compared to 74% in nondiabetic controls, according to US Renal Data System data between 1985 and 1993.49

Despite the concern for the development of premature cardiovascular disease (that may be exacerbated by the use of immunosuppressive drugs), data show that after renal transplantation, patient and graft survival are similar to those of matched controls. Aggressive management of cardiovascular risk factors is recommended pretransplantation and posttransplantation.49

Cardiac

Cardiac involvement is frequent and is caused by accumulation of glycosphingolipids in the myocardium, valves, and conduction system.

Time of onset and progression of cardiac involvement is unknown.

Cardiac manifestations have been reported in female carriers but they are usually uncommon and mild. Regardless of gender differences, involvement appears to increase with age.

Cardiomyopathy

Left ventricular hypertrophy in AFD is usually not associated with significant systolic or diastolic dysfunction. In later stages decreased left ventricular end-diastolic volume leads to decreased stroke volume and cardiac output.

Unlike other infiltrative diseases, there is evidence of left ventricular hypertrophy on electrocardiogram.

Rarely in the so-called “cardiac variant,” cardiomyopathy is the principle manifestation of AFD.

Valvular disease

Mitral valve thickening or prolapse is seen in young patients and may be accompanied by thickened papillary muscles while aortic valve and aortic root abnormalities typically appear in older patients.

There is no difference in valvular involvement among hemizygotes and heterozygotes, and severe valvular disease requiring surgery is rare.

Conduction system disease

Accumulation of lipids in the conduction system predisposes to tachyarrhythmias and bradyarrhythmias.

Coronary artery disease

More than 50% of hemizygotes and heterozygotes complain of anginal chest pain.

Endothelial dysfunction may play a major role in the development of symptoms.

Atherosclerosis is aggravated by hyperlipidemia and HTN that often accompany the disease.

Treatment

Novel, disease-specific therapies are being explored including the use of Galactose that acts as a competitive inhibitor of α-Gal A, or enzyme-replacement therapy.48,50

Neurologic and Other Manifestations

Cerebrovascular disease

Manifestations affect the posterior circulation predominantly.

Consists of large vessel ectasia and large- and small-vessel occlusive disease.

The presence of cerebrovascular disease indicates a poor prognosis with a high likelihood of recurrence or death for both hemizygotes (76%) and heterozygotes (55%).

Affected individuals have been noted to have a high incidence of both venous and arterial intravascular thrombosis.

Acroparesthesia

Constant burning pain and tingling of the toes and fingers and episodic bouts of severe neuropathic pains.
Pain is precipitated by change in temperature, exercise, or stress. It can be accompanied by fatigue, low grade fever, and joint pain. Peripheral neuropathy is common. The cause is thought to be accumulation of glycolipids in cutaneous and vasa vasorum vessels as well as small nerve axons. Phenytoin, carbamazepine, and/or gabapentin are given for symptomatic relief.

**Autonomic dysfunction**
- Abnormalities include decreased tear and saliva formation, abnormal cerebrovascular reactivity, cardiac arrhythmias, abnormal gastrointestinal motility, and pain perception.
- Accumulation of lipids in the autonomic ganglia of the intestine results in not only abnormal motility but also loss of haustral markings in the colon; diverticula develop as a consequence and may rupture, causing peritonitis.

**Ophthalmologic and Auditory Manifestations**
- Tortuosity of conjunctival and retinal vessels.
- Corneal opacities.
- Lenticular deposits.
- Vision is usually spared.
- Many patients develop asymmetric deafness caused by lipid deposition in the nerve cells of the cochlea. Sudden loss of hearing may be secondary to occlusion of a branch of the basilar artery to the cochlea.

**Neuropsychiatric Manifestations**
- Patients are at risk for chronic depression and narcotic dependence for treatment of neuropathic pain.

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**MEDULLARY CYSTIC KIDNEY DISEASE (MCKD)**

- Rare inherited cystic disease characterized by functionally and morphologically abnormal tubules leading to interstitial inflammation and fibrosis.
- Has an autosomal dominant inheritance:
  - MCKD1 was mapped to chromosome 1 (1q21) and accounts for the minority of cases.
  - MCKD2 was mapped more recently to chromosome 16 (16p12) and accounts for mutations in most cases.
- The current hypothesis is that the MCKD gene product might interact with nephrocystin and other binding proteins to form focal adhesion signaling complexes.

**Pathology**
- Affected individuals have normal- to small-sized kidneys.
- When cysts are found, they are located at the corticomedullary junction and in the medulla. However, the presence of cysts is not universal.
- Microscopically, there is diffuse tubulointerstitial inflammation characterized by areas of tubular atrophy interspersed with hypertrophied and dilated tubules. Glomeruli are usually normal and immunofluorescent stainings nonrevealing.

**Diagnosis and Clinical Course**
- Diagnosis relies on clinical features with a thorough family history. The presence of cysts supports the diagnosis but is not essential. Computed tomography scan is the most sensitive technique for cyst detection.
- The first signs are inability to concentrate the urine and salt wasting, leading to polyuria and polydipsia. Progressive renal failure ultimately leads to ESRD.
- MCKD presents on average at around 28 years of age and results in ESRD in the third to fifth decade. However, within the same family a large variability in age of onset and course of the disease can be observed.
- Transplantation is the treatment of choice. The disease does not recur in the transplanted kidney.

**MCKD and Associated Disorders**
- MCKD traditionally has been associated with juvenile nephronophthisis (NPH) because of similar clinical features and pathologic findings. However, unlike MCKD, NPH is detected in early childhood, may have associated extrarenal manifestations,
and leads to ESRD usually by the second decade of life. Moreover, NPH has an autosomal recessive inheritance, and the gene responsible for it has been mapped to chromosome 2 (2q13), making these 2 disorders unrelated. More recently MCKD has been associated with familial juvenile hyperuricemic nephropathy (FJHN).

Hyperuricemia caused by reduced fractional excretion of uric acid is the hallmark of FJHN and has been described in cases of MCKD.

Both disorders have an autosomal dominant pattern of inheritance and similar clinicopathologic features and course.

The identification of the FJHN gene on chromosome 16 (16p11.2), in close proximity to the MCKD gene locus, makes these 2 disorders potentially allelic.

References