



What is ARPKD/CHF?

A Brief Overview of ARPKD and CHF:

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare genetic disorder that affects approximately 1:6,000 to 1:40,000 persons in the general population, depending on the source of reference. There is a higher incidence in certain populations including the Finnish and Afrikaaner. ARPKD is a chronic progressive disease that results in kidney failure and liver abnormalities that includes fibrosis, hence the term Congenital Hepatic Fibrosis (CHF). It is neither contagious, nor affects intelligence. CHF has the potential to cause severe clinical liver complications. The age spectrum for onset of symptoms is from birth to adolescence, seldom adulthood. ARPKD is commonly diagnosed early in life; approximately 50% of cases are diagnosed prenatally.

There is no cure and neonatal death occurs in up to 50% of cases. Death is not from kidney failure, but from pulmonary hypoplasia (underdeveloped lungs) that is secondary to oligohydramnios (decreased amount of amniotic fluid). Ventilatory support may help the infant survive the newborn period after which, the chances of long-term survival improve substantially. There is potential for an excellent quality lifestyle with medical management.

The Cause of APRKD and CHF:

Abnormalities in a single gene (PKHD1) appear to cause greater than 99% of all ARPKD/CHF cases. It takes one of these defective genes from each parent for the "recessive" disorder to be present. As a fetus begins to develop, the formation of the kidneys and the liver are affected (ARPKD/CHF). The kidney collecting tubules/ducts are initially dilated and later become cystic. It is thought that in the liver ductal plate development is incomplete, this results in ductal plate malformation, dilatation, and fibrosis (scarring) of the portal tracts which carry blood to the liver and bile away from the liver. There may also be abnormalities in the portal vein.

For a recessive trait or disease to occur, both parents must carry and pass on the defective gene. Even though parents are "carriers" of the ARPKD gene, they never have symptoms or signs of the disorder. There is a 25% chance of

the disorder occurring with each pregnancy when the parents are “carriers” of the gene. Typically there is no prior family history of the disease.

Diagnosis and Findings:

It is now accepted that previous terms such as Infantile Polycystic Kidney Disease (PKD), Early Childhood PKD, Late Childhood PKD, Adolescent PKD, Juvenile PKD, Early Onset PKD and Adult PKD are incorrect. Since the genetic causes of polycystic kidney disease are now known, it is correct to say that a person has Autosomal Recessive Polycystic Kidney Disease (ARPKD) or Autosomal Dominant Polycystic Kidney Disease (ADPKD), or some other form of cystic kidney disease.

Fetal ultrasound may visualize large echogenic kidneys, also described as “bright”, from 13 weeks gestation, with low or absent amniotic fluid (oligohydramnios) beginning after 20 weeks gestation. There are however many instances where ARPKD is not visualized on sonogram until the 3rd trimester or after birth. A prenatal finding may also include absence of fetal bladder filling, although this finding does not always correlate with postnatal severity. Huge flank areas may complicate vaginal delivery. For those infants that are severely affected, Potter' facies or Potter's syndrome may be present. This is seen as deep set eyes, broad, flattened nose, abnormally small jaw bones, and low set ears; additionally, deformities of the extremities due to fetal restriction and compression caused by insufficient amniotic fluid occurs.

Kidneys can be grossly enlarged, their size peaking at 1 to 2 years of age, with stabilization at 4 to 5 years of age. With time, sonographic patterns change due to the progression of cysts and fibrosis, changing the typical kidney shape. Older patients may be mistakenly identified as having ADPKD. Contrast-enhanced computerized tomography (CT) has been effective in visualizing the collecting tubules, which are dilated in ARPKD. Ultrasounds have largely replaced intravenous pyelograms (IVP). Glomerular Filtration Rate (GFR) may improve during the first 6 months of life from kidney maturation. Approximately a third of the ARPKD population will need dialysis or kidney transplant by 10 years of age. However the decline in renal function is very variable and in some cases of ARPKD end stage renal failure (ESRF) does not occur until adulthood.

Amniocentesis and direct genetic testing cannot yet offer an ARPKD diagnosis. Prenatal testing is available for families who have had one confirmed ARPKD birth. This is an indirect diagnostic technique, based on gene linkage and the PKHD1 locus, and dependant on DNA from current or previously affected children and their parents. Diagnosis should be differentiated from other kidney disorders, including ADPKD, cystic dysplastic kidneys, glomerulocystic kidney disease, and medullary sponge kidney.

Differences Between ARPKD AND ADPKD/ Inheritance Patterns:

Autosomal Recessive Polycystic Kidney Disease is different from Autosomal Dominant Polycystic Kidney Disease. They are different disease processes with bilateral (two) cystic kidneys in common. Large cysts (macrocyts) are associated with ADPKD, located at any point along the nephron. Macrocyts have been found in ARPKD, but usually microcyts (less than 2 cm) are present and are located in the collecting tubules.

Relative renal size decreases with age in ARPKD, yet increases in ADPKD. Both are inherited disorders, but the inheritance patterns are different. The most commonly used prevalence rate is 1:400 to 1:1000 for ADPKD and 1:6,000 to 1:40,000 for ARPKD. ADPKD is passed on 50% of the time from one affected parent (parent with disease) with ~10-30% resulting from a spontaneous mutation and is considered a systemic disease, affecting a variety of different organs in different ways; ESRD is reached 50% of the time by 60 years of age.

As previously noted ARPKD is passed on 25% of the time with each pregnancy where both parents are “silent” carriers of a mutated gene. The child must receive a mutated gene from each parent for disease expression. Parents of children with recessive disorders are unaffected by the disease, or disease free, and there is a 50% chance that unaffected ARPKD/CHF full-siblings will be carriers of the mutated gene and 25% chance they will neither carry nor have the disease. When a person is only a carrier and has children with someone who is not a carrier, then there is a 50% chance each child will be a carrier and a 50% chance they will not be a carrier. If an individual **with** ARPKD has children with someone who neither has ARPKD nor carries the mutated gene, then all their children will be carriers of the “silent” gene. If an ARPKD individual has children with someone who carries the gene, with each pregnancy there is a 50% chance the child will carry the gene and 50% chance they will have the disease. If two ARPKD individuals have children, then there is a 100% probability that all their children will have ARPKD.

Early Newborn Period:

Almost everyone with ARPKD is diagnosed during infancy or childhood, with about 10% of children diagnosed after 5 years of age. The first signs of the disease vary greatly. Thirty to 50% of ARPKD infants die at birth or shortly thereafter, primarily as a result of underdeveloped lungs and pulmonary complications. This is because lung maturation is dependent on sufficient amniotic fluid being present during fetal lung development. Oligohydramnios (limited or no amniotic fluid) results in hypoplasia (underdevelopment) of the lungs. Besides the potential for poor lung development, neonates (less than 30

days of age) may be premature (less than 37 weeks gestation), have low serum sodium (salt) levels, and water imbalances. Renal function may be compromised during the newborn period, but death caused primarily by renal failure during the neonate period is extremely rare.

Huge cystic kidneys may impair a newborn's breathing effort or cause delivery complications. The infant may "grow into" and accommodate the massive size of the kidneys. Infants with true lung hypoplasia often die soon after birth from pulmonary insufficiency. At this time technology doesn't exist to prenatally determine which mechanically ventilated infants will have hypoplasia incompatible with life. Severe respiratory distress can be caused by reversible fluid overload, neonatal lung disease, or limited diaphragm movement from massively enlarged kidneys. In some instances selective nephrectomies have allowed room for lung expansion when severely limited diaphragm movement was due to kidney pressure. Respiratory complications include pneumothoraces, atelectasis, meconium aspiration, bacterial pneumonia, or surfactant deficiency.

Prognosis:

Prognosis, especially for those who survive the newborn period is far less bleak than once thought. Infants with ARPKD who survive mechanical ventilation have a good chance of survival. The 5-year survival rate is 80 to 95% for those who survive the neonatal period (pertaining to the first 4 weeks after birth). Because of improved ESRD (End Stage Renal Disease) treatment, and more effective control of both systemic and portal hypertension, survival into adulthood is common.

Correlation of disease symptoms with age at time of diagnosis has been suggested. It was thought that ARPKD individuals who were diagnosed early in life exhibited more kidney manifestations, with little, or sometimes no apparent liver involvement, while those diagnosed later in life, up to adolescence, (seldom into adulthood), manifested more clinical liver complications with little or no kidney manifestations. This description does not however take into account the prominent liver manifestations that occur in children with early kidney transplants who initially exhibited no liver problems.

Because of continued improvements in mechanical ventilation, neonatal support, control of hypertension, management of ESRD and transplantation, the ARPKD population is now living well into adulthood.

Clinical Features of ARPKD:

Children with ARPKD may produce large amounts of dilute (unconcentrated) urine and hence have polyuria (frequent urination) and polydipsia (excessive thirst). This is due to a concentrating defect related to small 1-2 mm fusiform

dilatations of the collecting tubules and collecting ducts. Bed-wetting is not uncommon in school-age children and is due to the concentrating defect. Children with ARPKD have increased risk of dehydration with prolonged fevers, vomiting or diarrhea, and during times of insufficient oral fluids intake. On hot summer days and during sport activities water bottles are needed to prevent dehydration.

Growth may be impaired and twenty-five to thirty percent of children with ARPKD/CHF experience failure-to-thrive. The exact cause is unknown, but possible reasons include decreased food intake secondary to increased intra-abdominal pressure, reduced food absorption because of GI motility abnormalities and chronic renal insufficiency. Hypertension may occur in up to 80% of children, is often severe and can develop in the first several months after birth. There is a strong relationship between hypertension and decreased renal function, however hypertension may present with normal renal function, or hypertension may be absent with ESRD. Hypertension is a factor in the progression of renal deterioration and without aggressive treatment severe hypertension can be life-threatening. The cause of hypertension is not clearly understood; possible explanations include reduced renal blood flow, activation of the renin-angiotensin system, or abnormal blood serum sodium handling. Hyponatremia (low serum sodium level) may result from defects in free water excretion (may spontaneously correct itself). Other serum electrolytes are generally normal and metabolic acidosis is not a significant feature of the disease.

Sixty to 100% of ARPKD patients have palpably enlarged kidneys. There is no treatment at this time to decrease kidney size. The enlarged kidneys may secondarily cause inguinal and umbilical hernias. ARPKD has no clear association with vesicoureteric reflux (VUR), bladder dysfunction or other GU anomalies. There is no definitive data to suggest that UTI's (urinary tract infection) have a higher than normal incidence in the ARPKD population. However white blood cells (pyuria) are often present in the urine without infection. Urine cultures should confirm and guide all antibiotic therapy.

Clinical Features of Congenital Hepatic Fibrosis:

Congenital Hepatic Fibrosis definition: **C**ongenital-meaning inherited, predetermined or present at birth, **H**epatic-pertaining to the liver (medical management determined by GI specialists/hepatologists), and **F**ibrosis-formation of fibrotic tissue or scarring.

CHF is malformation of the bile ducts and surrounding tissue that is also referred to as Ductal Plate Malformation. This malformation is associated with biliary ectasia (bile duct dilatation) and scarring of the liver in the portal tracts (which carry blood to the liver and bile away from the liver). It is uncommon for

a person to have CHF without ARPKD. However, if a person has ARPKD they always have some degree of CHF. The inherited genetic defect affecting the kidneys and liver is the same. CHF has a highly variable clinical course and there are no guidelines that predict the prognosis. Symptom presentation and severity varies greatly, from microscopic biopsy detection to severe clinical liver manifestations with complications.

The liver may be normal or enlarged in size. By ultrasound it is usually echogenic or coarse in appearance. Dilated intrahepatic biliary ducts, decreased visualization of peripheral portal veins or hypoplasia of the portal vein may be noted even in the neonate. As fibrosis progresses, hepatosplenomegaly (enlarged liver and spleen) develops along with ultrasound findings of patchy echogenicity.

The portal vein, which carries large amounts of blood to and through the liver, and the bile ducts, which carry bile away from the liver are both part of the “plumbing system”. They normally have unrestricted flow. Usually bile ducts are thin and hair-like in shape. In CHF, it is thought that fetal maturation of the portal tract and bile ducts is incomplete which results in an abnormal, bizarre configuration, hence ductal plate malformation. For some reason these areas fill with scar tissue (fibrosis) creating blood flow resistance and turbulence. This slows blood flow resulting in a “backup pressure” within the vessels that feed the portal vein. This backup pressure results in increased pressure in the portal vein (portal hypertension). When the blood flow obstruction is severe, blood flow may reverse, or may spontaneously by-pass (shunt past) the liver. These shunts manifest as swollen veins in the esophagus (esophageal varices), on the abdominal wall and around the rectum (hemorrhoids). Portal hypertension is different to high blood pressure that can be measured with a blood pressure machine.

Doppler flow studies showing blood flow towards the kidneys (hepatopetal) may exhibit less portal hypertension pressure than the reversal of portal blood flow. Magnetic Resonance Cholangiography (MRC) is an effective non-invasive diagnostic tool for evaluating portal hypertension and the biliary tree.

Liver function tests usually remain normal. Even for symptomatic individuals, synthetic liver function generally is preserved, as the liver usually continues to excrete, synthesize, and regulate hormones and chemicals normally. As a child ages, fibrosis tends to progress. Liver failure and liver transplantation are not common, although severe liver involvement sometimes requires shunting or transplantation.

Subsequent Problems That Can Develop Due to Portal Hypertension:

Hepatomegaly (enlarged liver), splenomegaly (enlarged spleen due to increased pressure in the liver), esophageal varices (distended, weakened, and blood-filled veins under pressure, or sacs with a thin esophageal wall, having the potential to bleed suddenly and unexpectedly into the esophagus). Severe, abrupt bleeding of esophageal varices can cause the stomach to fill with large amounts of blood, causing bloody vomitus (throw-up). This is a life-threatening medical emergency due to the large loss of blood volume (see care of bleeding esophageal varices below). Proper care is needed immediately.

Portal circulation refers to the passage of blood in the portal vein, spleen and gastrointestinal tract (GI tract). Veins from the stomach and intestines, which feed the portal vein, may also be under pressure. Bleeding from the GI tract may result in stools that are bloody, black or tarry in consistency and medical care should be sought immediately.

Hypersplenism is an exaggeration of the hemolytic (blood destruction) function of the spleen and may develop with advanced splenic enlargement, resulting in deficiency of blood elements. Hypersplenism results in thrombocytopenia (low blood platelet count, utilized for blood clotting), anemia (low red blood count, oxygen carrying component of blood), and leukopenia (low blood leukocyte level, functions are complicated, but chiefly fight bacteria and other microorganisms).

Cholangitis is an infection of the bile and bile ducts with microorganisms and occurs due to bile sluggishness or stasis. Severe cholangitis can be life threatening. Caroli's syndrome or disease refers to cystic dilatation of segments or the entire intrahepatic biliary system that may be present with ARPKD. These persons are at an increased risk for cholangitis. The threat of cholangitis lessens with age, and not every child with CHF has Caroli's. Caroli's is associated with chronic cholestasis and liver stones in young ARPKD adults. There are a few documented cases of liver cancer associated with CHF that have occurred in adulthood that may be due to years of chronic inflammation.

Clinical Care Considerations:

The focus is to keep healthy and growing, treating manifestations as they occur. The accumulation of information here does NOT include all dimensions of clinical healthcare, does NOT provide medical advice, but is a resource and a continuous "work in progress", as we learn more about comprehensive, multi-disciplinary clinical care options.

NEWBORN STAGE:

Offer mechanical ventilation and support at birth to distinguish those with true pulmonary hypoplasia.

BLOOD PRESSURE CONTROL:

High blood pressure is often present during the first year of life. Poorly controlled hypertension is a major factor in premature renal function deterioration and if untreated may also lead to heart failure.

- Drugs available:
 - Angiotensin Converting Enzyme Inhibitors or ACE Inhibitors
 - Calcium Channel Blockers
 - Diuretics

FAILURE TO THRIVE (FTT):

For unknown reasons, approximately 25% of the children will experience FTT.

- Utilize anti-reflux measures
- In carefully evaluated and selected children, enteral or parenteral supplementation may be useful
- Growth hormone does work

AVOIDING CONTACT OR COLLISION SPORTS:

Because of the potential for blunt trauma or serious injury to enlarged organs, contact sports should be avoided, including football, wrestling, hockey, kick boxing, boxing, karate, and lacrosse. Sports like youth soccer, baseball, volleyball, and basketball are generally safe (although elbowing can be dangerous).

A spleen protector is not scientifically proven, and doesn't provide zero risk for activities such as bicycle riding (potential for handle bar injury), soccer and skiing, but if fitted and worn properly, provides a significant barrier to protect organs.

UTI (Urinary Tract Infection):

Abnormal urinalysis does not always indicate infection.

- Culture and treat infections promptly, utilizing antibiotic regimens
- Aggressive treatment may prevent additional scarring
- Avoid instrumentation of GU tract

CHOLANGITIS:

Ascending cholangitis can be a serious life-threatening complication.

Children with fever for 3 days without an identifiable source should be worked up for cholangitis. The evaluation includes blood cultures and one may consider a liver biopsy or aspiration for culture.

- Requires aggressive IV antibiotic therapy.
- Ursodeoxycholic acid (ursodiol) may assist in moving bile and may

prevent bile stasis

HYPERSPLENISM:

An exaggeration of the hemolytic (blood destruction) function of the spleen, resulting in deficiency of blood elements. Potential treatment may be needed for:

- **Thrombocytopenia** -low blood platelet count, the “sticky factors” of the blood utilized for blood clotting.
- **Anemia** - low red blood count, oxygen carrying component of blood. Low results may be due to hypersplenism or chronic renal failure. (Epoen replacement therapy is available).
- **Leukopenia** -low blood leukocyte level, function is complicated but chiefly fights bacteria and microorganisms.
- **Coagulopathy**-such as high prothrombin or PT level (vitamin-K supplements available).

THERAPY FOR PORTAL HYPERTENSION:

(The following information for Portal Hypertension and Care of Bleeding Esophageal Varices is by Dr. David Piccoli, Division Chief, Pediatric Gastroenterology and Nutrition, The Children's Hospital of Philadelphia.)

- **Medical Therapy:** Designed to decrease the pressure and volume in the portal system.
- **Sclerotherapy:** Injection of the esophageal varices to clot them and thicken the wall, so that flow will go in a different direction.
- **Variceal Ligation (Banding):** Placing rubber band ligatures around the dilated veins to help them clot and block flow. There is some evidence that variceal ligation has advantages over sclerotherapy in certain situations.
- **Surgical Shunts:** Taking the high pressure portal or splenic blood flow and plugging it into low pressure vessels.
- **Radiologic Shunts:** TIPS- making a connection between the high pressure portal vein and the low pressure hepatic vein.
- **Liver Transplantation**

CARE OF BLEEDING ESOPHAGEAL VARICES:

If Child:

- 1) Vomits blood
- 2) Vomits brown or black material which resembles coffee grounds, OR
- 3) Has a black, tarry or bloody stool

This is a potentially life-threatening event, due to massive GI bleeding and

hypovolemia (low blood volume).

IMPORTANT INITIAL MANAGEMENT:

Go to the nearest Emergency Room in your area or call 911. (If you are waiting for an ambulance to arrive, lie flat and elevate legs.)

INITIAL MANAGEMENT AT HOSPITAL:

- A large IV placed with the following studies drawn:
 - CBC with differential
 - Reticulocyte count
 - PT/PTT

- Type and cross for 2 units PRBC minimum
- Insert a nasogastric tube into the stomach, lavage with room temperature normal saline to verify the presence of blood. Tube left in place.

THERAPEUTIC OPTIONS:

- H2-blockers, proton pump inhibitors
- Admission to an ICU
- Systemic octreotide or vasopressin
- Esophageal ligation (banding)
- Esophageal variceal sclerotherapy
- Sengstaken-Blakemore Tube

- Emergency radiology TIPS shunt
- Laser Coagulation, Heater Probe, and Bicap
- Emergency Surgical shunt

MEDICAL THERAPY FOR ESOPHAGEAL VARICES:

Pitressin (vasopressin):

- Given as a continuous infusion in ICU or on transport
- Enhances systemic pressure with peripheral vasoconstriction
- Causes inappropriate ADH, hyponatremia, seizures
- An alternative is octreotide
- Nitrates

SCLEROTHERAPY:

(Injection of varices with a sclerosing agent)

Indications and uses:

- Active variceal bleeding
- Therapy following a bleed
- Prophylactic therapy

- Role in pretransplant therapy

Alternative to this therapy:

- Esophageal variceal ligation (banding)
- Medical therapy with beta blockers
- Surgical shunt therapy
- Expectant clinical care with no therapy

ESOPHAGEAL BANDING:

(Acute or chronic care of esophageal varices)

Technique:

- Upper endoscopy
- Suction to pull varix into chamber
- Manual firing of a band over the neck of the varix
- Spring loaded multiple rubber bands
- Band occludes varices

Advantages:

- Necroses and falls off after several days
- Minimizes or eliminates many of the risks of sclerotherapy

EMERGENCY TIPS:

(Transvenous (jugular) Intrahepatic Portosystemic Shunt performed by interventional Radiologists - making a connection between the high pressure portal vein and the low pressure hepatic vein.)

Technique:

- Access the hepatic veins
- Perforate through to the portal veins
- Dilate the channel
- Place a stent and then dilate the stent

Advantages:

- Can be performed emergently without surgery
- Does not require surgery of prehepatic vessels

Disadvantages:

- Common restenoses

PORTOSYSTEMIC SHUNTS:

(Reserved for repeated hemorrhages, significant pancytopenia secondary to hypersplenism and failure of sclerotherapy or banding.)

Technique:

- Portocaval shunt
- H-type mesocaval shunt
- Distal or proximal splenorenal shunt
- High likelihood of long-term success

Disadvantages:

- Major surgery
- Rearranges prehepatic vessels pre-transplant
- May clot with time
- Difficult or impossible in small infants
- Post-shunt encephalopathy may occur

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