



Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare genetic disorder affecting approximately 1 in 6,000 to 1 in 40,000 persons in the general population (although there is a higher incidence in certain populations e.g. Finnish and Afrikaaner). Symptoms occur from birth to adolescence, seldom adulthood.

There is no cure and many children die shortly after birth. However, for children who survive birth, there is potential for a high quality of lifestyle with careful medical management of the condition in adolescence.

ARPKD in infants

ARPKD is usually an **infantile disease** and an important cause of renal and liver-related sickness and mortality in children.

Almost everyone with ARPKD is diagnosed during infancy or childhood, with around 50% of cases diagnosed prenatally typically during an ultrasound (echogram) appointment. Ultrasounds can highlight large kidneys, also described as "bright", from 13 weeks gestation. After 20 weeks gestation, low or absent amniotic fluid (oligohydramnios) may be observable. A prenatal finding may also include absence of foetal bladder filling. As yet, amniocentesis and direct genetic testing cannot provide an ARPKD diagnosis. However, indirect genetic testing by linkage analysis can be accurate and is available on the NHS (ask your GP for details).

The first signs of the disease vary greatly. At birth, the infant's enlarged flank areas may complicate vaginal delivery. In the most severely affected children, Potter's syndrome may be present. This condition is characterised by deep-set eyes, a broad and flattened nose, abnormally small jaw bones, and low set ears. Additionally, deformities of the limbs and other extremities may occur, due to foetal restriction and compression caused by insufficient amniotic fluid.

30 to 50% of ARPKD infants die at birth or shortly thereafter, primarily as a result of underdeveloped lungs (pulmonary hypoplasia) and other pulmonary complications, rather than kidney failure. This is because lung growth is dependent on sufficient amniotic fluid being present during foetal lung development. Severe respiratory distress can be caused by reversible fluid overload, neonatal, lung disease, or limited diaphragm movement from massively enlarged kidneys. Other respiratory complications include pneumothoraces, atelectasis, meconium aspiration, bacterial pneumonia, or surfactant deficiency.

Infants may also be premature (less than 37 weeks gestation) and have low serum sodium (salt) levels and water imbalances.

Renal function may be affected during the newborn period (first 4 weeks) but death from renal failure during this time is rare. Huge cystic kidneys may impair a newborn's breathing effort.

Selective kidney removal (nephrectomy) may allow room for the lungs to expand where severely limited diaphragm movement is caused by kidney organ pressure.

ARPKD in children who survive the newborn period

If ventilation can be administered successfully to the infant, the chances of survival significantly increase. Prognosis, especially for those who survive the newborn period, is far less bleak than once thought. The 5-year survival rate is 80 - 95% for those who survive the first 4 weeks after birth. Because of improved renal treatment, and more effective control of hypertension (blood pressure), survival into adulthood is now common.

25 - 30% of ARPKD children, however, fail to thrive after birth. The exact cause is unknown, but possible reasons include decreased food intake secondary to increased intra-abdominal pressure, reduced food absorption because of gastro-intestinal motility abnormalities and chronic renal insufficiency.

ARPKD is chronic and progressive. Kidneys can be grossly enlarged, their size peaking at 1 to 2 years of age, with stabilization at 4 to 5 years of age. Older patients may be mistakenly identified as having Autosomal Dominant Polycystic Kidney Diseaseⁱ (ADPKD).

Children with ARPKD may produce large amounts of dilute (unconcentrated) urine and have polyuria (frequent urination) and polydipsia (excessive thirst). Bed-wetting is not uncommon in school-age children.

Children with ARPKD have increased risk of dehydration with prolonged fevers, vomiting or diarrhoea. On hot summer days and during sport activities water consumption is very important to prevent dehydration.

Hypertension may occur in up to 80% of children, is often severe, and can develop in the first several months after birth. The cause of hypertension is not clearly understood in ARPKD; possible explanations include reduced renal blood flow, activation of the renin-angiotensin system, or abnormal blood serum sodium handling. Hypertension is a major factor in the progression of renal deterioration and without aggressive treatment severe hypertension can be life-threatening.

Hyponatremia (low serum sodium level) may result from defects in free water excretion (and may spontaneously correct itself). Other serum electrolytes are generally normal and metabolic acidosis is not a significant feature of the disease.

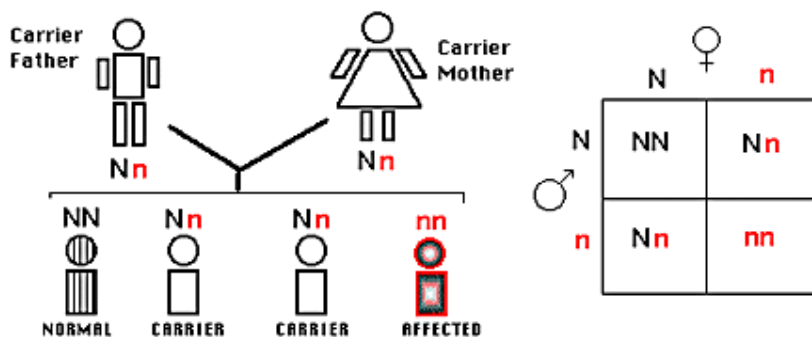
The genetics of ARPKD

Over 99% of all ARPKD cases are caused by abnormalities in a single defective gene called PKHD1, which encodes a protein known as fibrocystin or polyductin.

ARPKD is 'recessive' in a similar way to genetic diseases such as cystic fibrosis. This means the defective gene must be inherited from both parents for the disorder to occur. Each parent is a 'carrier' of one defective gene and therefore does not have ARPKD.

When both parents are carriers, there is a 25% chance of ARPKD occurring with each pregnancy, a 50% chance that their children will be carriers but not have ARPKD, and a 25% chance they will neither be carriers nor have ARPKD - see diagram below:

Recessive inheritance



(N = normal (wild-type) gene; n = mutant gene, e.g. in ARPKD N = a normal copy of PKHD1, n = the mutant, defective copy of PKHD1)

If a person with ARPKD has children with someone who neither has ARPKD nor is a carrier, then all their children will be carriers of the 'recessive' and defective gene. If an ARPKD individual has children with a carrier, then each pregnancy carries a 50% chance that the child will carry the gene and a 50% chance they will have the disease. If two ARPKD individuals have children there is a 100% probability that all children will have ARPKD.

Further information can be found on our website (www.pkdcharity.org.uk).

Alternatively, please visit the ARPKD/CHF Alliance (www.arpkd.org) website and the PKD Foundation website (www.pkdcure.org), both based in the US.

ⁱ Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common genetic disorders with a frequency of 1 in 500 to 1 in 1000. ADPKD symptoms normally occur in adulthood but an early manifestation can be confused sometimes with ARPKD, which is a separate and different condition.