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TITLE: **POLYCYSTIC KIDNEY DISEASE**

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POLYCYSTIC KIDNEY DISEASE

Definition

ADPKD is a systemic hereditary disorder transmitted by auto-somal dominant gene, characterized by renal cysts and commonly by hepatic cysts and abnormalities in the gastrointestinal tract and cardiovascular system.

Epidemiology

ADPKD occurs throughout the world. The prevalence in repor-ted series varies between 1:200 and 1:3000. Under the pioneer of the investigation of the disease O. Z. Dalgaard the prevalence is 1:1000.

Etiology

ADPKD is an inherited disease with an autosomal dominant mode of translation of the pathologic gene. So an individual with ADPKD must have the defective gene in one of a pair autosomal chromosomes. Therefore each offspring of an affected individual has a 50% chance of inheriting the chromosome carrying the de-fective gene and thus to inherit the disease.

In 1985 a major breakthrough occurred in the genetics of ADPKD. S.T. Reeders and associates localized for the first time the gene in the short arm of the 16th chromosome. The ADPKD-gene is closely linked to two normal genes, localized in 3'HVR and coding synthesis of alpha globin molecule and RBC- phosphogli-colat phosphatase respectively. The following studies found out that in 15% of families the gene is absent in such the region. In 1993 Peters and coworkers discovered the second gene localization in the long arm of the 4th chromosome. At this moment are in progress investigations of looking for the third ADPKD gene. The ADPKD gene in 16th chromosome has been dubbed /dъbt/ ADPKD-1, the ADPKD gene in 4th chromosome – ADPKD-2.

Pathogenesis

Too many investigations have been made and theories have been created to be explained the mechanisms of transformation of renal tubules into renal cysts. R. Virchow accepted in the middle of the XIXth century, that the main cause is the "inflammation" of tubu-lar epithelium, consequenced of tubular obstruction and fluid hy-persecretion. The longest survival belongs to the disembriogenic theory of Hildebrand from 1994. Under this theory during the em-bryonic development occurs a failure to unite metanephric blaste-ma with ureteral bud. Therefore the "blind ended" nephrons are transformed in cysts, because of cumulating of primary glomerular filtrate.

In 1964 two american scientists – E. Potter and V. Osatha-nondh on the basis of their precise microdissection study surely demonstrate, that "non-union" theory of Hildebrandh is absolutely wrong.

Now three main pathogenic factors have been identified – tubu-lar epithelium proliferation, fluid hypersecretion and accumulation and changed compliance of tubular basement membrane.

Clinical features

Proper symptoms of ADPKD. The disease starts after birth. The clinical demonstration is normally after age of 30 years. So the most of affected persons younger than 30 years are asymptomatic.

The symptoms related to ADPKD are: flank or back pain, hematuria, hypertension, enlarged kidneys and abdomen. Women may be symptomatic more than men.

Flank and back pain is the most common compliant. It can be mild or severe or disabling; continuous or intermitting; often is dull and nagging of quality. The mechanism of this pain is not defined finally, but it may be due to enlarged kidneys, pressure on the neighbour organs and chronic renal tract obstruction by the cysts.

Approximately 30-50% of patients have had hematuria. It can be microscopic or macroscopic. The hematuric episodes are more often in patients with enlarged kidneys and hypertension. Occasional patients required blood transfusion or nephrectomy.

Mild to moderate hypertension is the most common abnormality identified in physical examination. Its incidence vary between 50 and 70% and depends of the age and the renal function. The hy-pertensive persons have more heavy cystic disease than do nor-motensive subjects. Cystic deformation of the kidneys can even-tuate in hypertension by tubular disruption and salt handling with plasma volume expansion or intrarenal vascular disruption and renal ischemia, stimulating renin-angiotensin-aldosterone system (RAAS). Unfortunately several studies fail to show activating of RAAS.

One or both kidneys are palpable in approximately 50-90% of patients in older age group. Not uncommonly the kidneys are enor-mously enlarged. Although 25% of patients have only one, usually left, palpably kidney enlarged. On the average, men appear to ha-ve kidneys three times enlarged than those in women.

Urinalysis is abnormal in many patients. It appears hematuria, proteinuria - less than 1 g/daily, pyuria – in part of cases sterile.

Complications of ADPKD. Renal infection is often presented mainly as chronic pyelonephritis. Its incidence varies between 30-50% and it is more often in women. The other targets are cysts, bladder and perinephric tissue. The importance of pyelonephritis is connected with the faster deterioration of renal function in the same patients.

Renal calculi occur in 10-20% of ADPKD subjects.

Associated anomalies (AA)

The most often is the polycystic liver disease. Its incidence varies between 20 and 70%, in dependence of age and sensitivity of used methods. It appears that liver cysts are more common and larger in women.

Cysts in pancreas, ovaries, uterus lung, and brain occur at a much lower frequency, than in the liver.

The *second group* includes noncystic associated abnormalities. Intracranial aneurisms are the most important one. Its incidence has very wide variation.

Aneurisms involving the aorta have been reported rare.

Colon diverticula have been established in almost 80% of ADPKD patients undergoing dialysis and in 30% of non-ADPKD dialysis subject.

Different cardiac abnormalities have been described in ADPKD patients. The list includes valvular prolapse and valvular ring dila-tation, ruptured chordae tendineae and regurgitation. The most often involved are aortic and mitral valve.

The wide variety of associated organ abnormalities proves that ADPKD is a systemic disease, due to the defect in synthesis of collagen type IV.

Diagnosis

The main diagnostic criteria are many cysts in both the kidneys and a strong family history. The secondary diagnostic criteria are hepatic cysts, cysts in other organs, cerebral aneurisms, enlarged kidneys, and chronic renal failure. The definition of "many cists" means more than five cysts in every kidney. The hepatic cysts are "hallmark" for existence of ADPKD. The diagnosis is sure when the two main criteria are positive, or one main and two secondary cri-teria are presented.

The diagnostic program includes consequently usage of some diagnostic methods. The utiliz-ing of family history is invaluable. Unfortunately only 60-75% of patients have positive family history for ADPKD. This does not reflect a high spontaneous mutation rate for the gene, since the disease is found in one of more family members examined with sensitive ultrasonography in more than 90% of cases. This may be due in part of failure of physicians to inform patients about the hereditary diseases or of specific character of evolution of ADPKD in some of families.

The physical examination is very useful in part of patients. The both enlarged palpable kidneys with typical surface is a specific symptom. The combination with positive familial data allows rea-ching almost true diagnosis in part of patients. About 50% of per-sons suffering of ADPKD do not have palpable kidneys, although the positive palpable results increase with age. Of course the kid-ney palpation is inaccurate in determining the true renal size.

Given these limitations of history and physical examination in diagnosing ADPKD, the imaging techniques are the modalities used most frequently in establishing the diagnosis.

Ultrasonography (US) is the investigating method of choice, be-ing more sensitive than venous urography, while obviating /**o**bvieiting/ the exposure to radiation and contrast media and permitting the examination of liver and pancreas for cysts

Computed tomography (CT) is slightly more sensitive than US. Therefore CT is not preferred as an initial screening method. CT is indicated when US is not convincing for definite diagnosis or for discovery of some conditions – perinephric hemorrhage, calculi, perinephric abscess or renal carcinoma.

The imaging techniques, albeit sensitive and specific depend of cysts size, hence of the patient age. This prer**e**quisite precludes the diagnosis of gene carrier state before the appearance of renal cysts. The gene linkage analysis and use of DNA restriction mar-kers added powerful new diagnostic tool, wich depends only on genotype, not the phenotype. There must be a sufficient number of family carriers to permit the description of the polymorphism that travels with the ADPKD gene in the tested family. The affected and unaffected members must carry different marker types. In the large family the gene can be deduced with more certainty. In fact DNA-analysis may be used to determine the gene status of a fetus. The last appliance reveals a new possibility to diagnosis ADPKD before birth and to take a prophylaxis of the disease with the agreement of affected parents.

Treatment

Etiologic therapy is impossible at the moment. It is possible to take the prophylaxis using prenatal gene testing. This possibility has low practical value because the high price of linkage probes and because of psychological reasons.

Pathogenic devices are in the stadium of scientific-experimental investigations.

Symptomatic therapy includes antihypertensive drugs. The ACE inhibitors are devices of choice. The use of other medication is wide accepted – beta-blockers, calcium antagonists, diuretics.

Hemodialysis is the usual mode for treatment of CRF. For patients with only moderately enlarged kidneys peritoneal dialysis can also be utilized.

Renal transplantation is too useful for ADPKD patients, as for other ESRD subjects. The need of pretransplant nephrectomy is not definitive. Only some small studies indicated a high frequency of ADPKD-related infections and sepsis after transplantation. The incidence of posttransplant malignancy in native kidneys has not been determined.

It does not appear, that the kidneys transplanted in ADPKD recipients are at higher risk for cyst formation.