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AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

(monograph)

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Annotatsiya

Autosomal dominant polikisoz buyrak kasalligi muammosining dolzarbligi, bu bolalar va kattalardagi keng tarqalgan irsiy buyrak kasalliklaridan biridir. Regressiya tahlili natijasida surunkali pielonefrit bilan og'rigan ADBP mavjud bolalarda buyrak uzunligining yillik o'sishi pielonefrit kasalligi mavjud bo'lmagan bolalarga qaraganda ko'proq ekanligi aniqlandi. ADBP va gipertoniya bilan og'rigan bolalarda ultratovush tekshiruvi bo'yicha buyraklarning o'rtacha uzunligi va kistlarning maksimal diametri gipertoniya bo'lmagan bolalarga qaraganda sezilarli darajada kattaroqdir.

Аннотация

Актуальность проблемы аутосомно-доминантной поликистозной болезни почек, это один из распространенных наследственных кистозных заболеваний почек у детей и взрослых. В результате регрессионного анализа установлено, что ежегодный прирост длины почек у детей с ADPKD, имеющих хронический пиелонефрит, больше, чем у детей, не имеющих пиелонефрит. Средняя длина почек и максимальный диаметр кист по ультразвуковом исследовании у детей с ADPKD и артериальной гипертензией достоверно больше, чем у детей без артериальной гипертензии.

Annotation

The relevance of the problem of autosomal dominant polycystic kidney disease is one of the most common hereditary cystic kidney diseases in children and adults. As a result of regression analysis it was found that the annual increase in kidney length in children with ADPKD who have chronic pyelonephritis is greater than in children who do not have pyelonephritis. The average kidney length and the maximum cyst diameter according to ultrasound in children with ADPKD and AH are significantly greater than in children without AH.

LIST OF ABBREVIATIONS

AH- arterial hypertension

AP - arterial pressure

ADPKD - autosomal dominant polycystic kidney disease

AA - amino acid

ACE - angiotensin converting enzyme

ARPKD - autosomal recessive polycystic kidney disease

IA - intracranial aneurysm

DNA - deoxyribonucleic acid

RRT - renal replacement therapy

CDC - consultative and diagnostic center

ABB-Acid-base balance

CT - computed tomography

MRI - magnetic resonance imaging

VUR - vesicoureteral reflux

PC1 (2) - polycystin 1(2)

PCR - polymerase chain reaction

EGFR - epidermal growth factor receptor

GFR - glomerular filtration rate

TRF- terminal renal failure

Ultrasound - ultrasound examination

CKD - chronic kidney disease

cAMP - cyclic adenosine monophosphate

EGF - epidermal growth factor

K/DOQI – Kidney Disease Outcomes Quality Initiative

KDIGO - Kidney Disease: Improving Global Outcomes

OMIM - Online Mendelian Inheritance in Man

PKD1 (2) - polycystic kidney disease 1(2)

TNF-a - tumor necrosis factor – a

RELEVANCE

Polycystic kidney disease ranks first among renal pathologies in terms of clinical severity and number of complications. Polycystic kidney disease is a hereditary disease characterized by autosomal dominant transmission.

The relevance of the problem of autosomal dominant polycystic kidney disease, one of the common hereditary cystic kidney diseases in children and adults, is due to the peculiarities of the development and growth of cysts, the inability of existing treatment methods to prevent the increase in the size of cysts and kidneys, and the progressive impairment of kidney function pathology. In the occurrence and growth of renal failure to its terminal forms, the leading role is played by chronic pyelonephritis, which always accompanies polycystic kidney disease, often proceeds latently with periodic exacerbations. The latter is associated with the most frequently used conservative therapy aimed at stopping the inflammatory process in polycystic kidneys.

Based on this, differential diagnostics of renal masses is relevant because early diagnostics determines the outcome of the disease. Clinical examination of patients with renal polycystic disease, early recognition of renal failure and hypertension as complicating factors and adequate therapy for a long time provide a relatively satisfactory condition and, to a certain extent, the ability to work of patients.

CHAPTER I. ETIO - PATHOGENESIS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Cystic kidney diseases are a clinically and genetically heterogeneous group of diseases that may first manifest themselves both in the prenatal period of life and in adulthood. Hereditary cystic kidney diseases are one of the common causes of terminal renal failure in children.

§1.1. Hereditary cystic kidney disease

Polycystic kidney disease (Polycystickidneydisease) is a hereditary disease characterized by the formation of multiple cysts in the parenchyma of both kidneys, without signs of dysplasia [15,25].

According to the type of inheritance, a distinction is made between autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) [23].

ADPKD is a systemic disease characterized by progressive cystic dilation of the renal tubules and extrarenal manifestations in the form of cystic lesions of other organs, valvular heart abnormalities, vascular pathology, and abdominal wall hernias [33]. The incidence rate ranges from 1:400-1:1000 live births, which is approximately 12.5 million patients worldwide [17]. ADPKD ranks third (after diabetes mellitus and hypertension) in the list of diseases leading to the development of terminal renal failure [9].

§1.2. Genetic features of ADPKD

ADPKD is genetically heterogeneous; in 85% of cases it is caused by a mutation of the PKD 1 gene (MIM 601313), and in the remaining cases by a mutation of the PKD 2 gene (MIM 173910).

Cases of trans-heterozygous inheritance with mutations in both (PKD 1 and PKD 2) genes have been described, which are more severe, and yet patients reach adulthood [5,15]. Earlier studies suggested that homozygous mutations in both PKD 1 and PKD 2 are incompatible with life [24,29,33]. However, homozygous and compound heterozygous patients with ADPKD 1, and patients with mosaicism

have been recently described. These cases may play a role in the very early development of ADPKD and partially explain the pronounced intrafamilial variability of the disease [21,24].

PKD 1 is a fairly large gene (52 kb) consisting of 46 exons, the length of the encoded transcript is 14 kb , located at 16p 13.3 [16,35]. It is known that three quarters of the 5' end of the gene (exons 1-33) are repeated approximately 6 times on the same chromosome 16, in the form of highly homologous (with an identity of - 95%) pseudogenes, which complicates genetic testing of PKD 1 [31,41].

PKD 2 gene is located on chromosome 4 (4 q 21- q 23), the length of the encoded transcript is 5.4 kb . Despite its large length (-68 kb), its genomic structure is much simpler - it consists of 15 exons, and it does not have highly homologous pseudogenes [34].

The PKD 1 and PKD 2 genes are the proteins polycystin 1 (PC1) and polycystin 2 (PC2), respectively. PC1 (460 kDa) and PC2 (110 kDa) are members of the TRP (transientreceptorpotential) ion channels, therefore also called TRPP 1 and TRPP 2 (Transient Receptor Potential Polycystic). Despite some similarity in structure and the same nomenclature, SD2 is a more typical representative of this family of ion channels, and PC1 is a distant homologue of TRP [41,47].

PC1 is a large membrane glycoprotein consisting of 4303 amino acids (AA), has the structure of a receptor or adhesion molecule and contains the following parts: an extracellular NH2 -terminal domain (~3074 AA), a cytoplasmic COOH-terminal domain (-197 AA) and 11 transmembrane domains (1032 AA). The C-terminal domain contains a coiled-coil region, through which it interacts with the C-terminal region of PC2, providing stabilization of the latter [41]. It is suggested that PC1 and PC2 represent a signaling complex of a receptor and an ion channel that regulates key cellular processes of growth, differentiation and orientation in the epithelial cells of the renal tubules. Polycystins are associated with each other: disruption of the function of one polycystin leads to a change in the second [7]. PC1 interacts with a variety of other proteins through different sites located in both the cytoplasmic and extracellular domains. PC1 is present in the kidney, brain,

heart, bone, muscle, and bronchi [26]. Its expression in the kidney appears to be age-dependent, with peak levels in the late fetal and early neonatal periods; after birth, PC1 expression declines sharply [45]. The main synthesis of PC 1 in the kidneys occurs in the epithelium of the distal tubules and collecting system [11,34]. It should be noted that, despite the possibility of developing cysts in ADPKD from all parts of the nephron, in practice cysts in most cases develop from the collecting system. Basically, PC1 is found on the lateral membranes of cells - in places of intercellular connections, in primary villi and in desmosomes [34,68].

PC2 (968 AK) is a non-selective cation channel permeable to Ca^{2+}. With the help of PC2, intracellular Ca^{2+} is released both directly in response to a local increase in the concentration of this ion, and indirectly, through the effect on two main intracellular Ca^{2+} channels: the ryanodine receptor and the 1,4,5-triphosphate receptor [4,17]. PC2 consists of short cytoplasmic N-and C-terminal regions and 6 transmembrane segments, the last 5 of which have a structure strictly corresponding to that of the TRP channel, and between the fifth and sixth segments there is a putative cleft for the passage of ions [38]. GTZ2 interacts with a large number of different proteins, including, as already noted, with PC1 [50,62]. PC2 is present in the kidneys, heart, ovaries, testicles, vascular smooth muscle and in the small intestine [20]. In the kidneys, it is detected in all parts of the nephron, with the exception of the thin part of the loop of Henle and the glomerulus. In the distal parts, the expression of PC2 is more pronounced than in the proximal ones. Basically, PC2 is localized in the primary villi of the renal tissue, in the membrane of the endoplasmic reticulum [13,49,71]. Unlike PC1, PC2 expression is relatively stable throughout life [21].

It is noteworthy that cysts in ADPKD develop focally, and only 1-5% of nephrons are involved in this process. To explain this fact, the "two-hit" hypothesis was proposed [2]. According to it, the "first hit" is a generative mutation in one of the two copies (alleles) of PKD 1 or PKD 2. This is not enough for a given cell to change phenotypically and become cystic, since the second allele functions normally. A cyst occurs only when a somatic mutation of the second "normal"

allele occurs in a given cell - the "second hit". This is confirmed by the detection of somatic mutations in the PKD 1 and PKD 2 genes in the tissues of the kidney and liver of patients with ADPKD. This phenomenon is also called "loss of heterozygosity " (LOH) [29]. It has been proven that with such a mechanism of cyst development, a complete absence of polycystin is not necessary. Apparently, there is a certain threshold level of expression, and when the amount of protein is below this level, the mechanism of cyst development is triggered. At least for PC1 this fact has been proven [6,37]. Paradoxically, there are studies indicating that overexpression of polycystins is also accompanied by the development of cysts [9,48]. There is no explanation for this phenomenon yet.

Subsequently, a lot of data appeared that do not allow us to explain the focal development of cysts only by " two hit " mechanism. In all likelihood, there is an additional trigger point. Studies on rodents have shown that, depending on the stages of the animal's development at which the third damaging agent was applied, the prevalence of the lesion, the timing of cyst development, and the parts of the nephron from which cysts most often arise, differ. When lesion occurs in the embryonic period, the vast majority of cysts develop from the collecting area of the nephron, and in the postnatal period - from the loop of Henle. Perhaps this is due to the different proliferative potential of tissues at different periods of development [30,42]. It has also been shown that the frequency of cyst development is much higher if the damaging agent acts on a newborn animal, compared to a more mature one. This means that polycystins play a very important role in the process of rapid growth and division of renal tubule cells, and the loss of their function during this period leads to the development of cysts [24,35].

Consequently, the third trigger for cystogenesis in ADPKD is damage to the epithelial cells of the tubules, since it initiates the inclusion of reparative processes, that is, rapid growth and division of cells, which, with impaired function of polycystins, proceeds excessively actively and ends not with the restoration of the damaged area, but with the development of cysts [51,82]. This may be one of the reasons for the occurrence of new cysts during life in patients with ADPKD, since

the probability of occurrence of various obstructive and ischemic lesions increases with age. This discovery is very valuable, since it provides a key to preventing disease progression. This hypothesis is confirmed by the work of Kolesnikova IF (2000), which showed rapid growth of cysts in children with ADPKD who have pyelonephritis [46,56]. Another possible explanation for the appearance of new cysts is the gradual accumulation of somatic mutations during life [14,35,60].

§1.3. Genetic influence on the ADPKD phenotype

ADPKD 1 (mutation in the PKD 1 gene) is more severe than ADPKD 2 (mutation in the PKD 2 gene). All publications on cases of early-onset ADPKD for which the causative gene is known are associated with PKD 1 [12,27]. The prevalence of hypertension is 4 times higher in the population with ADPKD 1, urinary tract infections and hematuria are also more often detected in this [19]. The incidence of intracranial aneurysms (IA) and severe polycystic liver disease is approximately equal in ADPKD1 and ADPKD2 [3,32,58].

With ADPKD1, patients reach end-stage renal failure (ESRF) ~ 20 years earlier (53 years) than with ADPKD2 (69 years) [32]. According to M. Barua et al. (2009) the severity of the disease can predict which gene is involved in the development of the disease - PKD 1 or PKD 2: if there is a patient with ADPKD in the family who developed terminal renal failure before the age of 55, then there is a high probability (sensitivity 72%, PCR 100%) of having a mutation in the PKD 1 gene, but if - after 70 years, then - in the PKD 2 gene (sensitivity 74%, PCR 100%) [8].

It has been shown that at the same age, the kidney size in ADPKD 1 is much larger than in ADPKD 2, and a large kidney volume is associated with rapid disease progression. However, it has been shown that although the annual increase in cyst volume is greater in ADPKD 1 than in ADPKD 2 (74.9 ml and 32 ml, respectively), the rate of increase in cyst volume is not statistically different (5.68% and 4.82%, respectively). This means that the severity of ADPKD 1 is explained by the fact that more cysts occur at an earlier stage of the disease, and not because existing cysts increase in size faster. Therefore, PKD 1 and PKD 2

genes regulate cyst formation, not cyst enlargement: the cystogenesis process consists of a gene-dependent cyst development phase and a gene-independent cyst enlargement phase [10,31,43]. Early cyst development in ADPKD1 is consistent with the “two - hit” model of cystogenesis, since PKD 1 is a major target for mutations.

It was also revealed that in ADPKD 2 there are gender differences in the time to reach end-stage renal failure (ESRF): in men, on average, 68 years, in women - 76 years, while in ADPKD1 no differences were noted [28,75]. To date, 1923 mutations of the PKD 1 gene and 241 mutations of the PKD 2 gene are known (Tables 1 and 2).

Table 1

PKD 1 and PKD 2 genes (compiled according to ADPKDMutation) (2012)

Gene	Total number of mutations	Pathogenic mutations
PKD 1	1923	927 (48.2%)
PKD2	241	167(69.3%)

Table 2

Quantitative ratio of different types of pathogenic mutations in the PKD 1 and PKD 2 genes (compiled according to ADPKD) (2012)

Type of mutations	PKD1		PKD2	
	Pathogenic mutations 927		Pathogenic mutations 167	
	Obviously pathogenic 619	Likely pathogenic 308	Obviously Pathogenic 129	Likely pathogenic 38
Frameshift	310	-	61	-
Nonsense	203	-	40	-
Splice	62	29	23	8

deletions and large deletions	34	41	3	4
Insertions	9	8	1	-
Substitutions	-	230	-	26
large duplication	1	-	1	-

There is still no clear answer to the question of whether the characteristics of the course and prognosis of the disease depend on the type and localization of mutations in the PKD 1 and PKD 2 genes. S. Rossetti et al. (2002) found that the severity of the disease depends on the position of the mutation in the PKD 1 gene. In this study on 324 patients with ADPKD 1 from 80 families, it was shown that 5' localization of mutations leads to the development of end-stage renal failure 3 years earlier than 3' localization (53 and 56 years, respectively), but a direct dependence on the type of mutation has not been established [33,68]. It is also known that patients with 5' terminal mutations are more prone to intracranial aneurysms (ICA), especially those who had hemorrhagic strokes before the age of 40 or have a family history of this pathology [44]. In 461 patients with ADPKD 2 from 71 families, no dependence of the phenotype on the type and localization of mutations was found [16].

§1.4. Modifying factors

In ADPKD, there is significant intrafamilial variability of disease symptoms. For example, S.Geberth et al. (1995) showed in parent-child pairs that ESRD can develop in children either 26.3 years earlier or 27.2 years later than in their parents [5]. Analysis revealed that the age of reaching terminal renal failure in siblings and dizygotic twins is more variable than in monozygotic twins, which speaks in favor of genetic predisposition [18,42].

Many studies have been published on the effects of candidate genes. Although earlier publications reported that the DD variant of the I / D polymorphism of the angiotensin-converting enzyme (ACE) gene is associated with a more severe course of ADPKD, a subsequent meta-analysis of data from a large number of

studies devoted to this problem showed that this polymorphism does not affect the outcome of the disease [25,52]. In Tazon - Vega et al. (2007) published the results of a study aimed at identifying the association of polymorphisms of seven candidate genes (NOS 3 - endothelial nitric oxide synthase, ACE - angiotensin-converting enzyme, TORB - tumor growth factor pi, BDKRB 1 and BDKRB 2 - bradykinin receptors 1 and 2, EGFR - epidermal growth factor receptor and PKD 2) with the age of development of ESRD in 355 patients from 131 families with ADPKD1. No significant association of disease progression with any of them was established [15,36].

§1.5. The role of non-genetic factors

It is obvious that non-genetic factors also influence renal and extrarenal manifestations of ADPKD. This is evidenced, for example, by the fact that cystic liver disease is more severe in women, especially those taking hormonal contraceptives, estrogen replacement therapy, or with a history of multiple pregnancies [23,80]. It is believed that in men with ADPKD the rate of increase in cyst size is higher than in women, and ESRD in ADPKD 2 occurs earlier in men, which indicates the role of sex hormones as factors that can influence the course of the disease. It has been proven that caffeine can increase the production of cAMP in cyst-forming cells, thereby stimulating proliferation and fluid secretion [47,54]. Smoking is also a risk factor for more rapid progression of renal disease and ESRD, especially in men [40]. Obesity promotes the development of proteinuria and ESRD. The effects of dietary changes in patients with ADPKD, such as reduced protein intake or the use of flaxseed oil, which have shown positive results in animal models, have either not been confirmed or have not been studied at all in humans [53,68].

§1.6. Pathogenesis of cyst development

In the pathogenesis of cyst development, the following play a key role [30]:

- impaired expression and function of EGFR (epidermal growth factor receptor);
- a decrease in the amount of intracellular Ca^{2+}, with deviations in the

intracellular CAMP signaling system;

- disruption of the structure and/or function of primary cilia;
- changes in cell-cell and cell-matrix interactions.

These pathogenic processes underlie three fundamental causes of the development and progressive expansion of cysts, which are [2,11]:

1) tubular cell hyperplasia
2) predominance of secretion processes over absorption processes
3) disruption of the structure and/or function of the extracellular matrix of the tubules.

(Detailed pathogenesis is described in Figure 1.) Hyperplasia of tubular cells with expansion of the tubular wall area is the most important factor in the development and expansion of cysts. An increased ability to proliferate epithelial cells of both cystic and visually unchanged renal tubules has been shown in individuals with ADPKD. In stimulating the processes of proliferation of tubular epithelial cells, cAMP, EGF, and EGFR play an important role [6,47].

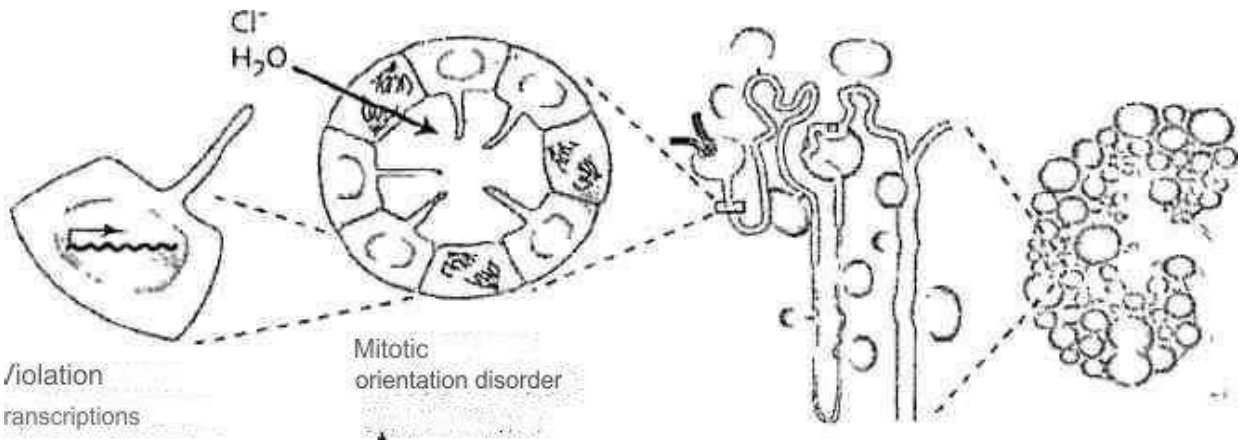


Figure 1. Cyst development at the cell, nephron, and kidney levels [12]. Defects in the genes encoding the PC1 and PC2 proteins disrupt transcription, leading to abnormal cell proliferation and ion secretion, which causes the formation of fluid-filled cysts.

In cystic kidneys, excessive expression of EGFR and its dislocation to the apical membrane of cystic cells were detected, and EGF was detected in large quantities in the cystic fluid, while in tissues, EGF expression was reduced [40]. The role of apoptosis in cyst formation has been proven: the imbalance between

apoptosis and proliferation processes is of key importance [12,48].

Cyst fluid consists of glomerular filtrate only in the early stages of ADPKD, while the cyst is connected to the tubule [9,29]. When the cyst reaches ~200 (0.2 mm) in diameter, it is isolated from the tubule and further increases in size occur due to the mechanism of transepithelial chloride secretion mediated by cAMP [9,17]. Chloride enters the cell via the basolateral Na+-K+-Cl^{2-} cotransporter and accumulates in the cytoplasm. The chloride channel (CFTR - cystic fibrosis transmembranereceptor) on the apical membrane of the cell ensures the transition of chlorides into the cyst cavity, then sodium accumulates in the cavity, which in turn ensures the flow of water through aquaporins [33].

In many inin vivo and inIn vitro studies have shown the role of quantitative and qualitative changes in Na^+ - K -ATPase activity in the development and expansion of cysts. It is assumed that in ADPKD, an increase in Ca^{2+}-K^+-ATPase activity in the proximal tubules through increased secondary active transport (for example, secretion of organic anions) leads to osmotic accumulation of fluid [50]. There are reports that in the collecting ducts, Na^+ - K^+-ATPase is located not on the basolateral surface, as in normal cells, but apically, which can lead to a change in the direction of Na^+ and water transport and provoke fluid accumulation in the cyst cavity [1,16,26]. However, according to other authors, the polarization of Na^+.

K-ATPase secondary to chronic ischemia. Due to the expansion of cysts, compression of blood vessels occurs, and areas of hypoperfusion occur, which leads to the development of fibrosis [7].

The third important reason for the development and expansion of cysts are disturbances in the extracellular matrix of the tubules. Diffuse ultrastructural and biochemical disturbances in the basement membrane of the tubules have been described. Specific defects in the biosynthesis and transport of proteoglycans, expression of laminin-alpha, collagens I, III and IV types, metalloproteinases in the matrix and their inhibitors in the tissue have been revealed [4,12,15]. In vitro epithelial cells of tubules of individuals with ADPKD produce much more

extracellular matrix than normal cells, which in turn disrupts the microenvironment of epithelial cells, leading to increased hyperplasia and secretion [7,16]. It can be assumed that the mechanism of cyst formation is quite simple: due to reduced elasticity of the basement membrane, the tubules expand under normal intratubular pressure. However, everything is much more complicated: cysts occur due to the fact that disruption of the matrix structure leads to disruption of cell-matrix interaction. This interaction regulates many processes - cell growth and differentiation, expression of proteins on the cell surface, gene expression. Probably, disrupted cell-matrix interaction enhances the processes of epithelial cell hyperplasia and secretion of intracystic fluid [25,42].

Signs of increased vascularization around the cysts and a continuous process of new vessel formation are shown. It is assumed that angiogenesis is also involved in the pathogenesis of cyst enlargement in ADPKD: it provides the increasing needs of cystic cells for nutrients with growth, is responsible for increased vascular permeability, promoting the secretion of fluid into the cyst [25,80].

Pathological processes in the interstitium, leading to interstitial inflammation and fibrosis, as well as a decrease in the protective effect of antioxidant systems, contribute to the progression of renal damage in ADPKD [35].

It has been proven that polycystins are localized in special structures that perceive signals from the extracellular environment, such as primary cilia, adhesin complexes. Their function is very important in the regulation of intracellular Ca^{2+} homeostasis, and disturbances in this homeostasis and in the cAMP signaling system play a central role in the pathogenesis of ADPKD [42].

Recently, much attention has been paid to the role of primary cilia. ADPKD belongs to the so-called ciliopathies (cilia - cilium) - a group of genetic disorders that occur as a result of mutations in the genes responsible for the synthesis of proteins associated with cilia [42]. They are thin, long, motionless protrusions of the apical part of the membrane of epithelial cells, and are found in all parts of the nephron. Normally, in the tubules, cilia protrude into the lumen and perform a sensory function. In this, the main role belongs to the PC1-PC2 complex, which

perceives mechanical and chemical stimuli and converts them into a current of Ca^{2+} through the PC2 channel. This in turn leads to the release of Ca^{2+} from intracellular reserves (the exact mechanisms of this process are not yet known). In ADPKD, cystic cells lose the signaling system, their Ca^{2+} reserves in the endoplasmic reticulum are depleted, which, unlike normal cells, does not cause a reciprocal influx of Ca^{2+} and, accordingly, the intracellular concentration of Ca^{2+} also decreases. Violation of intracellular Ca^{2+} homeostasis leads to the accumulation of cAMP, which in turn promotes the development and growth of cysts due to the activation of cellular proliferation and stimulation of CFTR -mediated secretion of chlorides and fluid [31]. Despite the fact that under normal conditions cAMP suppresses cell proliferation, with a lack of Ca^{2+} it enhances this process [4,]. Subsequently, cell proliferation can be supported by FER-like factors present in the cystic fluid, insulin-like growth factor-1, detected in cystic tissue and through activation of mTOR (mammalian target of rapamycin). It has been shown that the mTOR kinase protein, the activation of which leads to cell hyperplasia, is involved in the pathogenesis of ADPKD [15].

§1.7. ADPKD CLINIC

Signs of kidney damage in ADPKD are: impaired renal function, arterial hypertension, pain syndrome and renal failure. All these manifestations are directly related to the development and increase in size of cysts in the kidneys [37].

Signs of impaired renal function in ADPKD

A decrease in the ability to concentrate is a fairly common symptom of ADPKD and is found in both adults and children [23]. The cause may be deformation of the kidney structures by cysts, resistance of the cortical collecting tubules to vasopressin, and a decrease in the amount of aldolase needed to create a countercurrent gradient [28]. It is suggested that decreased concentrating ability and increased blood vasopressin levels may contribute to the development of cysts, hypertension, and progression to ESRD, as well as contribute to the development of glomerular hyperfiltration, which is common in children and young adults [14,16,25,37].

Patients with ADPKD may have signs of distal tubular acidosis. Even with normal SCF, they have a defect in urinary ammonium delivery due to disruption of the corticomedullary structure by cysts and loss of the corticomedullary concentration gradient. Decreased tubular excretion of ammonium leads to a compensatory increase in cortical ammonium production. Increased ammoniogenesis and the resulting metabolic disturbances are thought to contribute to the development of new cysts. Local synthesis of autocoids, cytokines, and growth factors as a result of ammonium-induced complement activation and renal interstitial inflammation may contribute to abnormal epithelial cell growth and/or increased fluid secretion by them [,14,19,22,34]. Decreased excretion of ammonium and citrates, coupled with low urine pH, leads to the formation of urate and oxalate kidney stones.

Recent studies have shown that nephrolithiasis in ADPKD is more common (20% of patients) than in the general population, and the incidence increases with age [43]. However, the detection of stones and calcifications in the renal parenchyma and cyst walls is more effective with CT scanning, since ultrasound, in most cases, misses them. A direct correlation has also been found between kidney volume and the predisposition to stone formation in patients with ADPKD [34].

Arterial hypertension (AH) is one of the most common and early signs of ADPKD. It mainly develops before a decrease in the glomerular filtration rate (GFR) is detected [39]. A predictor of the development of hypertension is a decrease in renal blood flow, which can be recorded even before an increase in systolic and diastolic pressure [29].

AHoccurs in 60% of adult patients with normal renal function and in 10-30% of sick children [21,27].

hypertension diagnosis is 32 years in men, 34 years in women and 13 years in children. The presence of hypertension in a parent with ADPKD significantly increases the risk of its development in a child [46,50]. When comparing adults and children with ADPKD, with and without hypertension, similar in age and body

weight, the kidney volume in the first group was larger [13,70]. Moreover, in children with arterial hypertension, the rate of increase in kidney volume is twice as high as in children with normal blood pressure. According to [18], in children with borderline hypertension (>75 percentile) over 5 years, severe hypertension develops in 52% of cases [18].

Pathogenesis of hypertension development in ADPKD

Possible pathogenesis of the development of hypertension in ADPKD, pathogenesis is described in Figure 2. [36].

The most important role in the development of arterial hypertension is played by the activation of the intrarenal renin-angiotensin system, both in response to local ischemia due to compression by cysts, and due to hyperplasia of renin-secreting cells along arterioles and in the cyst wall [38,62].

Intracystic fluid of patients with ADPKD contains high levels of renin and other components of the renin-angiotensin-aldosterone system (RAAS) - angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin II receptor, and angiotensin II peptide itself. Other factors contributing to hypertension include increased activity of the sympathetic nervous system, imbalance of endothelial vasoactive mediators (overproduction of endothelin 1 and deficiency of nitric oxide), and dysfunction of polycystins (PC1 and PC2 are synthesized in smooth muscles and vascular endothelium).

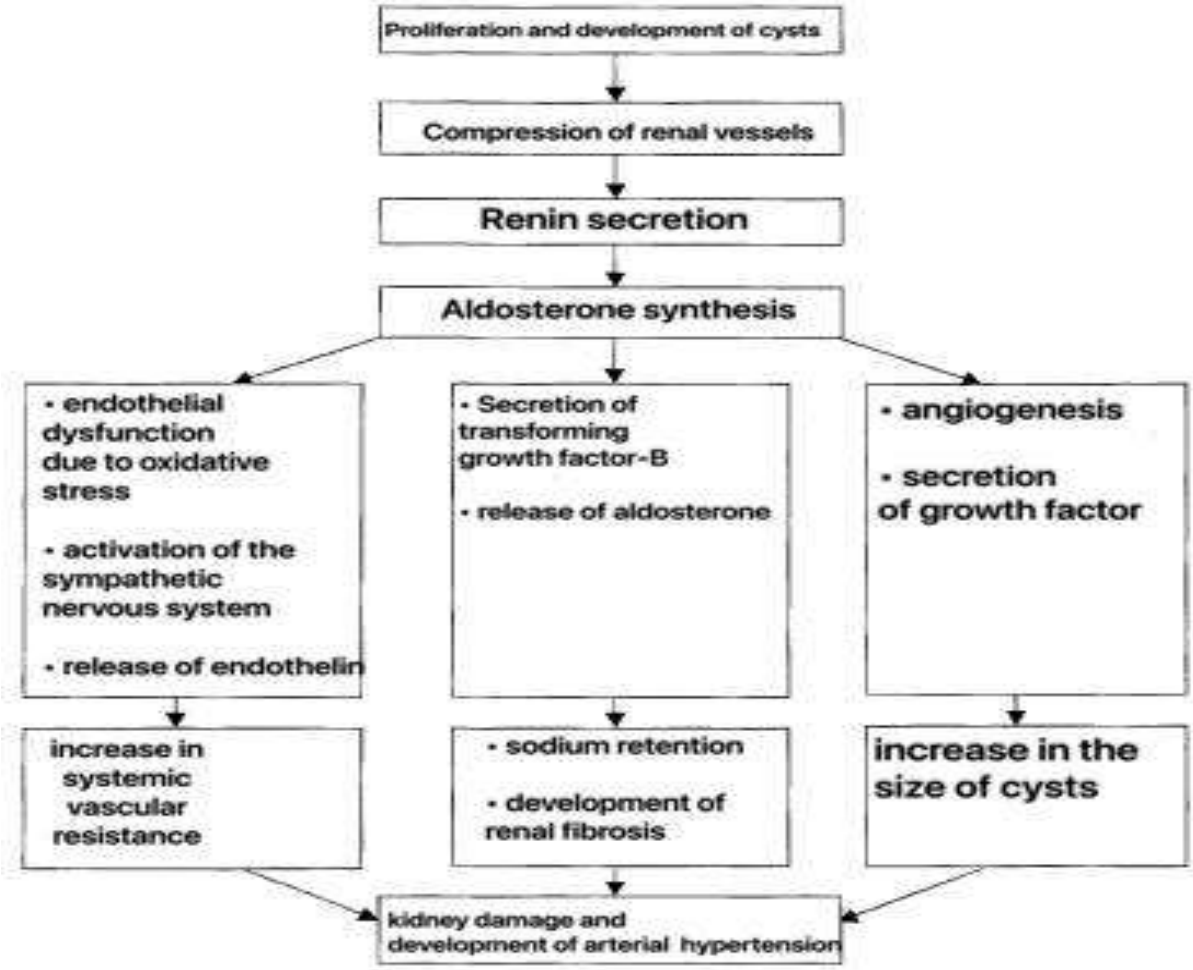


Figure 2. Pathogenesis of the development of hypertension in ADPKD.

Uncontrolled hypertension is a risk factor for the development of proteinuria, hematuria, rapid decline in renal function; increased morbidity and mortality from valvular heart disease and aneurysms; development of complications for the fetus and mother during pregnancy [44,47]. The development of hypertension before the age of 35 is associated with the outcome in ESRD on average 14 years earlier than with later development [49].

One of the most formidable consequences of prolonged hypertension is left ventricular hypertrophy, which in itself is a very significant risk factor for cardiovascular morbidity and mortality, accounting for 44% of all mortality cases in patients with ARPKD [10]. The relationship between hypertension and left ventricular hypertrophy, both in adults and children with ARPKD, has been shown in numerous publications [3,32]. According to one of them, a higher left

ventricular mass index, compared to normotensive children, was found not only in children with severe hypertension (AP>95 percentile), but even in children with borderline.

Level of hypertension (AP>75 percentile) [8]. In adult patients, left ventricular hypertrophy is diagnosed at about 40 years of age in 37-46% of cases. It is noteworthy that j of them do not have severe hypertension [14].

Pain is the most common symptom in adult patients with ADPKD (~ 60%). In children, pain syndrome, as the only clinical sign, occurs in 24-25% of cases [22]. Pain can be chronic and acute. Chronic pain is associated with growing cysts causing stretching of the renal capsule and partial occlusion of the collecting system [44]. Acute pain is associated with cyst hemorrhage, passage of stones, cyst infection. Sometimes the pain is very severe, associated with retroperitoneal bleeding and requires urgent medical intervention.

§1.8. Renal failure

Despite the continuous growth of cysts, in most patients the SCF remains within the normal range until the sixth decade of life [5,25]. By the time the SCF begins to decrease, the kidneys are usually significantly enlarged and deformed. From the moment of renal dysfunction, the SCF decreases at an average rate of 4.4-5.9 ml/min/year [24].

Various mechanisms are involved in the process of renal function decline in ADPKD: compression of normal renal parenchyma by growing cysts, vascular sclerosis, interstitial inflammation and fibrosis, apoptosis of tubular epithelial cells [9]. A recent study by Danish scientists has shown a connection between the age of development and low birth weight: according to their data, each missing kilogram of birth weight brings closer by 1.7 years [48,].

Risk factors for disease progression are mutation in the PKD 1 gene, male gender, development of hematuria before age 30 and hypertension before age 35, size and, especially, volume of the kidneys. In this regard, ADPKD1 is a more severe disease than ADPKD2, since with ADPKD1 the kidneys are significantly larger in size, however, the reason is not in the rate of increase in cyst volume (it is

approximately the same in both cases), but in the fact that patients with ADPKD1 develop a greater number of cysts at the same age than patients with ADPKD2 [21]. It has been shown that the total volume of the kidneys and the volume of cysts grow exponentially (in geometric progression) and the average increase is 5.3% per year [2].

Renal vascular resistance is known to be an independent predictor of renal function decline. This highlights the importance of vascular remodeling in disease progression and may explain cases where renal function decline appears disproportionate to the severity of ADPKD [39,50].

It has been shown that in terminal renal failure, the concentration of erythropoietin in the plasma of patients with ADPKD is on average 2 times higher than in patients with non-cystic causes. It is assumed that the reason for the stimulation of erythropoietin synthesis is regional hypoxia of the renal parenchyma, due to compression by cysts, the release of erythropoietin RNA by cyst cells (the concentration of erythropoietin in the cyst cavity is 4 times higher than in plasma) [30].

§1.9. Extrarenal manifestations

Polycystic liver disease is the most common extrarenal manifestation of ADPKD, occurring in both PKD 1 and PKD 2 mutations [50]. Cysts arise due to excessive proliferation and dilation of the bile ducts and peribiliary glands. The development of cysts is facilitated by estrogens (there are estrogen receptors in the cyst epithelium) [14], as well as growth factors and cytokines secreted into the cystic fluid [7]. In children, cysts in the liver rarely develop. Ultrasound examination may underdiagnose liver cysts. MRI examination has shown that the incidence increases with age: in the group of patients aged 15-24 years - 58%, 25-38 years - 85%, 35-46 years - 94% [34]. Liver cysts develop on average ten years later than kidney cysts [11]. In women, polycystic liver disease develops at an earlier age and is more severe than in men [26]. Risk factors include multiple pregnancies, oral contraceptives, estrogen replacement therapy, age, and severity of renal damage [43,56].

Liver cysts in ADPKD are virtually asymptomatic and never lead to liver failure. Standard laboratory tests do not reveal any abnormalities [19]. Complaints arise when the affected part of the liver reaches a certain volume or when complications develop. "Volumetric" symptoms include shortness of breath, bloating, decreased appetite, gastroesophageal reflux, back and/or abdominal pain. Sometimes cysts can compress the v. cavainferior, v. portae, bile ducts and provoke the development of signs of obstructive jaundice [4]. Complications include infection, hemorrhage and rupture of cysts.

Pancreatic cysts occur in approximately 10% of cases, their course is mostly asymptomatic, but in rare cases they can be accompanied by recurrent pancreatitis [53]. Therefore, pancreatitis should be taken into account in the differential diagnosis of abdominal pain in patients with ADPKD.

According to some data, colon diverticula are an extrarenal manifestation of ADPKD, since in this group of patients with ESRD, diverticula are more common than in other renal pathologies, but not all authors confirm this [1,18]. Duodenal diverticula are also often encountered, but a complete association with the disease has not yet been proven [27].

Cysts in the seminal vesicles occur in 40-60% of cases, sometimes leading to infertility. Another cause of infertility in men with ADPKD is impaired sperm motility [37].

Arachnoid cysts occur in approximately 8% of cases and are generally asymptomatic. However, there is an opinion that they increase the risk of developing subdural hematomas [10].

In patients with ADPKD, compared to the general population, hernias of the anterior abdominal wall are more common: inguinal in 13% (versus 4%), umbilical in 7% (versus 2%). This predisposition should be taken into account when considering the issue of renal replacement therapy, since hernias can interfere with peritoneal dialysis [6].

In the study by J. Driscoll et al. (2008), bronchiectasis detected by CT was three times more common in the group of patients with ADPKD than in the control

group of patients with other chronic kidney diseases (37% and 13%), respectively). This is due to a disruption in the synthesis of the GTTT1 protein in the motor cilia of the respiratory epithelium [49].

ADPKD can also be combined with neurogenic dysfunction of the bladder, nephroptosis, vesicoureteral reflux, and nephrotic syndrome [32].

Cardiovascular lesions are the most important non-cystic manifestations of ADPKD. They include: aneurysms of the intracranial and coronary arteries, less commonly - dolichoectasis, dilation of the aortic root, dissection of the thoracic aorta and arteries of the neck and head, pathologies of the valvular apparatus of the heart.

Intracranial aneurysms (IA) occur in an average of 8-10% of cases of ADPKD. There is a clear dependence of the frequency of IA on family history: if there are cases of IA and subarachnoid hemorrhage in the family, the frequency of occurrence is ~ 22%, if not - 5% [13]. No dependence on age, gender, presence of hypertension, or renal dysfunction has been established [40].

Most HF in ADPKD are asymptomatic, focal signs such as nerve palsy or seizures occur due to compression of specific structures by the enlarged aneurysm. Transient ischemic attacks are also possible due to aneurysm embolism or compression of nearby vessels [40].

Patients with ADPKD may be at high risk of developing vasospasm and transient ischemic complications after cerebral angiography, as well as central retinal artery and vein occlusion, which may be associated with arterial wall remodeling and increased vasoconstriction in response to adrenergic stimulation [28].

Valvular heart abnormalities are often diagnosed in patients with ADPKD, especially in the adult population: mitral valve prolapse (25-26%), mitral insufficiency (30-31%), tricuspid insufficiency (15%), aortic valve insufficiency (8%), tricuspid valve prolapse (6%) [22,25]. Divy et al. showed that mitral valve prolapse is 4 times more common in children with ADPKD than in their healthy siblings (12% and 3%, respectively) [41]. According to various publications, the

cardiovascular system is involved in the pathological process early, since even in young patients with ARPKD, with normal blood pressure and preserved renal function, left ventricular hypertrophy, diastolic ventricular dysfunction, endothelial dysfunction, thickening of the carotid artery walls, and inadequate increase in blood pressure in response to exercise may occur [8]. In view of such a variety and frequency of cardiovascular lesions, echocardiographic examination of patients with polycystic kidney disease is indicated, especially in the presence of noise during auscultation.

In patients with ADPKD, pericardial effusion is sometimes detected, which in most cases is not clinically manifested and is well tolerated by patients [3].

§1.10. ADPKD in children

The spectrum of clinical manifestations in children with ADPKD is very wide, from prenatal ultrasound diagnosis of massively enlarged kidneys and oligo/anhydramnios with possible perinatal death due to respiratory failure, to incidental findings of cysts in children who do not have any symptoms. There is a definition of "very early onset" (VEO - veryearlyonset), when the disease manifests itself before 18 months of age [45,74]. Individual cases of morbidity and mortality in the peri/neonatal period are practically no different from severe forms of A DPKD 1. Considering the prevalence of diseases (ADPKD-1/400-1/1000; ADPKD 1/20000), it can be calculated that the number of patients with early onset ADPKD is approximately similar to the number of patients with ARPKD. Unlike ARPKD, in which small fusiform cysts may be presented as small granular inclusions (salt and pepper symptom) on ultrasound, ADPKD is characterized by the presence of relatively large cysts, even in young children [45,79]. In cases of early development of ADPKD, there is an increased risk of the same course of the disease in the patient's siblings, due to the commonality of modifying factors in the family [12].

In children, the involvement of the kidneys in the pathological process may be uneven, and sometimes even one-sided. This concerns both the occurrence of cysts and an increase in the size of the kidneys [24]. With ADPKD1, cysts are detected

in 60% of cases before the age of 5, in 75-85% of cases - at the age of 5-18 years [33].

It has been shown that tubular function in children suffers much earlier than glomeruli: signs of decreased concentrating capacity appear long before changes in glomerular filtration [15]. Decreased glomerular filtration is generally not typical for children, with the exception of rare (4-5%) cases of development of terminal renal failure before adulthood (in children with very early onset of the disease) [38]. More typical is the occurrence of glomerular hyperfiltration, which compensatorily develops in intact nephrons. However, glomerular hyperfiltration is associated with glomerular hypertension and can simultaneously be a damaging factor. In this regard, it may make sense to prescribe drugs that level out vasoconstriction of the efferent arteriole. Proof of the advisability of prescribing RAAS system blockers for these purposes requires further prospective randomized studies [5]. Thus, glomerular hyperfiltration can serve as an early marker of the disease, since it is possible for it to develop already by the average age of 10 years in children [24]. Glomerular hyperfiltration is associated with a more rapid decline in kidney function and an increase in kidney size [17].

AH тoccurs in 20-30% of sick children, on average, at the age of 13 years [17,35].

Pain syndrome in children is less common and, as the only clinical symptom, occurs in 24-25% of cases [8].

The frequency of urinary syndrome (in the form of proteinuria and/or macrohematuria) varies from 10% to 38%, depending on the severity of kidney damage [13].

Cysts in other organs in children are not as common as in adults, but can occur even in the first year of life [43].

Risk factors for progression in children include early increase in kidney size, large number of cysts (10 or more before 12 years), arterial hypertension above the 75th percentile (taking into account height, weight, gender) [14]. According to the publication of Helal I., Reed B., Schrier R. W. (2012), early markers of the disease

(and therefore risk factors for progression) in patients of all ages are: total kidney volume, arterial hypertension, glomerular hyperfiltration, renal blood flow disorders, microalbuminuria, increased uric acid in the blood, and a number of biomarkers in the urine [40].

Diagnosis of ADPKD. Diagnosis of the disease in most cases is based on pedigree analysis and kidney imaging using ultrasound, CT or MRI. However, cyst development is an age-dependent process, so in individuals under 30 years of age, as well as in those with ADPKD2 (which has a later onset and a milder course), ambiguous ultrasound data or false negative results may occur [31]. In such cases, molecular genetic testing is justified for a more accurate diagnosis, the significance of which is especially high for the assessment of potential kidney donors. With the development of new approaches to the treatment of ADPKD, the effectiveness of which will be higher the earlier they are prescribed, there will be a need for the earliest possible diagnosis, even before the development of cysts in the kidneys, and accordingly, the relevance of molecular diagnostics for ADPKD will increase even more [23].

Ultrasound examination of the kidneys is the most common method for diagnosing ADPKD due to its high diagnostic accuracy, safety, general availability and, importantly, relatively low cost. Until recently, the diagnostic criteria of Ravine [31] were widely used for individuals with a 50% (presence of the disease in relatives of the 1st and/or 2nd degrees of kinship) risk of ADPKD, however, due to the heterogeneity of the disease, the sensitivity of these criteria was significantly reduced in cases of mutation in the PKD 2 gene [5]. In this regard, in 2009, new, unified criteria for ultrasound diagnostics of ADPKD were developed for individuals with a 50% risk [7]. Table 3 presents the Ravine criteria and unified criteria for ultrasound diagnostics of ADPKD.

Table 3

Criteria for ultrasound diagnostics of ADPKD for individuals with a 50% risk.

Age	Criteria	Feelings	Specificity	PCPR [1]	PCOR [2]

(years)		telnost			
Ravine Criteria					
15-29	>2 cysts*	84.8	99.4	99.2	87.7
30-39	>2 cysts in each kidney	82.8	100	100	87.5
40-59	> 2 cysts in each kidney	90	100	100	94.8
>60	> 4 cysts in each kidney	100	100	100	100
Unified criteria					
15-29	>3 cysts*	81.7	100	100	85.5
30-39	>3 cysts*	95.5	100	100	96.4
40-59	>2 cysts in each kidney	90.0	100	100	94.8
>60	>4 cysts in each kidney	100	100	100	100

*one-sided or two-sided

For children with a 50% risk under 15 years of age, according to various authors, the presence of 1 or 2 cysts (unilateral or bilateral) in the kidneys was considered diagnostically significant [51]. According to the latest data, for this age group with a 50% risk, the presence of large kidneys with high echogenicity, even in the absence of distinct macroscopic cysts, is diagnostically significant [23]. Since the disease is inherited in an autosomal dominant manner, if cysts of unknown etiology are detected in a child, an ultrasound scan of the parents is necessary to clarify the diagnosis.

PPPV - positive predictive value (PPV - negative predictive value)

If there are no cysts on ultrasound in parents under 30 years of age, it is necessary to examine the grandparents as well. In cases where the presence of ADPKD in the parents can be excluded (one cyst or no cysts in individuals aged 40 years or older) and paternity is not in doubt, it is necessary to consider the possibility of a denovo mutation (8-10% of all cases of ADPKD). In this case, the risk of developing ADPKD for subsequent generations is minimal (except for the presence of germline mosaicism in one of the parents) [47].

In cases where it is necessary to evaluate individuals with a 50% risk as potential kidney donors, the criteria for excluding this diagnosis are extremely

important. In the group of individuals over 40 years of age, such a criterion is the absence of cysts in the kidneys or the presence of only one cyst (PCR 100%). In the group of 30 to 39 years, the absence of cysts in the kidneys has a very high prognostic value, but does not completely exclude the diagnosis (PCR 99.3%). In the group of individuals under 30 years of age, genetic testing is necessary to exclude the diagnosis [24]. It is important to emphasize that the above criteria have been developed only for ultrasound diagnostics of ADPKD.

For imaging methods such as CT or MRI, whose resolution is several times higher than that of ultrasound, these criteria are not applicable.

Molecular diagnostics of ADPKD. Linkage analysis requires the participation of at least two (and preferably several) affected family members, which is not always possible. Accordingly, if there is only one affected person in the family and in cases of denovo mutations, the use of this method is impossible.

Direct DNA sequencing is the most suitable method of investigation and provides detection of mutations in =78-90% of cases [2,39]. However, due to the fact that most mutations are unique to a particular family, and one-third of detected PKD mutations are missense variants, the pathogenicity of some changes is difficult to prove.

Deletion-duplication analysis. To detect deletions/duplications, methods such as qualitative polymerase chain reaction (PCR), long-range PCR, multiplex ligation can be used. dependentprobeamplification (MLPA), arraygenomic hybridization. The frequency of detection of deletions/duplications is ~4% in PKD 1 and ~1% in PKD 2 [22].

Treatment of ADPKD. Treatment of dominant polycystic kidney disease is mainly symptomatic and is limited to blood pressure control and strict correction of arterial hypertension, pain relief with drugs or, if necessary, surgery - cyst aspiration, cyst sclerotherapy, surgical decompression and nephrectomy (used only in patients with end-stage renal failure, in the presence of severe pain), treatment of complications (cyst infection, cyst ruptures) [29]. As noted by Badani et al. (2004), surgical decompression does not affect the progression of the disease and does not

improve renal function, so it cannot be performed for this purpose [42]. In the development of ESRD, standard methods of renal replacement therapy are used - peritoneal dialysis, hemodialysis, kidney transplantation.

It is possible that in the near future pathogenetically based therapy of ADPKD will be introduced, which will prevent the development and growth of cysts and improve kidney function. Today, a large number of drugs affecting different links in the pathogenesis of ADPKD (somatostatin analogues, vasopressin V_2 receptor inhibitors, EGFR-tyrosine kinase inhibitors, mTOR inhibitors , cyclin-dependent kinase inhibitors, TNF - a inhibitors , ACE inhibitors, angiotensin receptor blockers, statins) are undergoing animal testing, and some of them (Table 4) are in phase III controlled clinical trials [10].

Table 4

Drugs for pathogenetic therapy of ADPKD that are undergoing phase III controlled clinical trials [31]

Preparation	Pharm.group	Target	Links
Octreotide Lapreotide	Long-acting somatostatins	Decrease quantities cAMP	[31]
Tolvaptan	V2 receptor antagonist	Decrease quantities cAMP	[8]
Sirolimus (Rapamycin) Everolimus	Immunosuppressants	mTOR inhibition	[12]
Pravastatin	Statins	Antiprolife ration impact	[20]
Lisinopril / Telmisartan	ACE inhibitor/angiotensin receptor blocker	Antiprolife ration impact	[41]

Given the rapid development of new treatment approaches, it is of utmost importance

is establishing a diagnosis at an early age, when there are no clinical manifestations of the disease yet, therefore, in the future, molecular diagnostics of ADPKD should become more accessible to treating physicians. Such an accurate diagnostic method will allow pathogenetic therapy to begin from an early age, and not for all family members, but only for those who inherited the mutant gene.

CHAPTER II. MATERIALS AND RESEARCH METHODS

§2.1. Contingent of examined patients and scope of the study

The work was carried out at the ASMI clinic in the Department of Surgery and Urology.

The study was conducted on the basis of a study of official medical records: the child's development history (form 112/u), the outpatient medical record (form 026/u), the inpatient medical record (form 003/u) and patient examinations.

generally accepted in domestic and foreign literature was used: autosomal dominant polycystic kidney disease. In the ICD, revision X (1998), the code for autosomal dominant polycystic kidney disease is Q 61.2.

According to international recommendations [31], the diagnostic criteria for adolescents with a 50% risk (the presence of the disease in a first-degree relative) aged 15 years and older were the unified criteria for ultrasound diagnostics of ADPKD (Table 5).

For children with a 50% risk under 15 years of age, according to various authors, the presence of 1 or 2 cysts (unilateral or bilateral) in the kidneys was considered diagnostically significant [12,31,43]. According to the latest data, for this age group with a 50% risk, the presence of large kidneys with high echogenicity, even in the absence of distinct macroscopic cysts, is diagnostically significant [7,19]. In this age group with a 50% risk, we considered the presence of 2 cysts in the kidneys (unilateral or bilateral) as a diagnostic criterion.

Table 5

Ultrasound diagnostic criteria for ADPKD for individuals with a 50% risk

Age	Criteria	Sensitivity	Specificity	PCPR [1]	PCOR [2]
15-29	>3 cysts*	81.7	100	100	85.5 96.4
30-39	>3 cysts*	95.5	100	100	94.8 100
40-59	>2 cysts in each kidney	90.0	100	100	
>60	>4 cysts in each kidney	100	100	100	

*- one-sided or two-sided

[1-] positive predictive value

[2-] negative predictive value

In the absence of a family history of polycystic kidney disease, but in the presence of enlarged kidneys and a total of 5 or more cysts in both kidneys in the proband, the presence of a denovo mutation was assumed [32,53].

Ultrasound examination of urinary system organs of 138 members of 71 families, in which at least one child was admitted with the diagnosis of "polycystic kidney disease" by the referring institution, was evaluated. The presence of kidney cysts was not confirmed in 6 probands. One proband was diagnosed with "Potter IV type cystic left kidney due to ureteral obstruction". One proband was found to have a solitary multilocular cyst of the lower pole of the left kidney. The diagnosis of "polycystic kidney disease" was confirmed in 98 members of 30 families: 52 children and adolescents (probands) aged 3 months to 18 years and 46 adults (parents) aged 30 to 55 years. A genealogical analysis of 30 families was performed to establish the type of inheritance of polycystic kidney disease. In 28 families, a clear dominant inheritance was observed (the presence of the disease in at least two generations: in relatives of both sexes of the first (parents, siblings) and/or second (grandmothers, grandfathers, uncles, aunts) degree of kinship).

In 16 families, it was not possible to clearly establish the type of inheritance due to the absence of the disease in relatives of the 1st and/or 2nd degree of kinship. In 5 of 16 probands with an unspecified type of inheritance, due to the presence of bilateral multiple cysts (more than 6) in the kidneys, the presence of a denovo mutation was assumed and they were included in the main study group (Figure 2.1).

As a result, the study included 98 members (52 children and adolescents and 46 adults) of 30 families with autosomal dominant polycystic kidney disease. Among the children and adolescents (probands) were 22 boys and 30 girls aged from 3 months to 18 years.

Among adults (parents) - 20 men and 26 women aged 30 to 55 years.

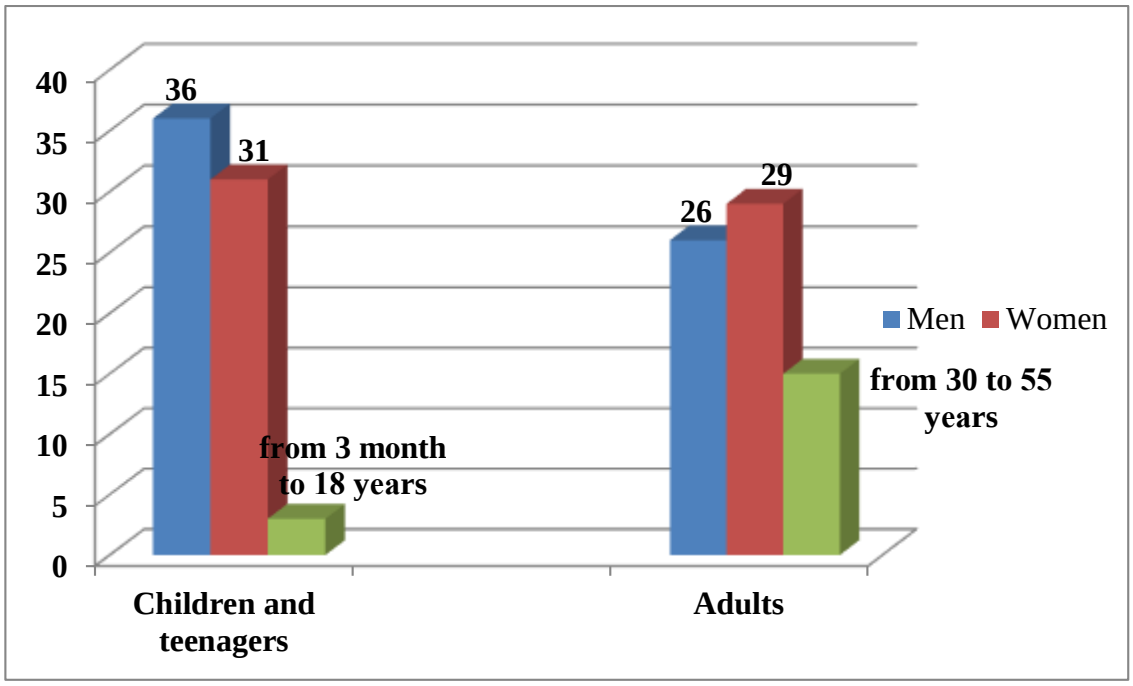


Figure 3. Total number of examined patients

The average age at the time of the first detection of kidney cysts was 8.24±0.64 years, maximum 16.58 years, minimum 1 month. The average age at the time of diagnosis of polycystic kidney disease was 9.52±0.65 years. The average age at the time of follow-up was 13.2±0.54 years, maximum 18 years, minimum 1.5 years. The time from the time of the first detection of kidney cysts to the time of follow-up in 67 patients ranged from 1 year to 18 years. The frequency of visits during this period ranged from 2 to 13 times. In the course of our study, laboratory and instrumental studies were performed on an outpatient basis for adult family members at their place of residence.

A follow-up study of 52 children and adolescents (probands) with ADPKD was conducted to determine the age at the time of first detection of renal cysts, the structure of extrarenal manifestations, the characteristics of clinical manifestations at the time of first detection of cysts and at the time of follow-up, the characteristics of the dynamics of cyst enlargement and kidney size, outcome and survival. In 46 adults (parents) with ADPKD, the frequency of arterial hypertension syndrome, extrarenal cysts, outcome and survival were analyzed. The scope of the study included:

1. genealogical, clinical and laboratory methods;

2. assessment of renal function: SCF based on endogenous creatinine clearance in the Rehberg-Tareev test and the Schwartz calculation formula, Zimnitsky test and blood acid-base balance;

3. Ultrasound (kidneys, liver, spleen, pancreas, ovaries; assessment of kidney volume based on ultrasound biometry). When calculating kidney volume, the truncated ellipse formula was used [47]:

Kidney volume (cm^3) = length x width x thickness x 0.053;

4. Computer tomography (kidneys, liver, spleen, pancreas, brain) or magnetic resonance imaging (kidneys, liver, spleen, pancreas, brain);

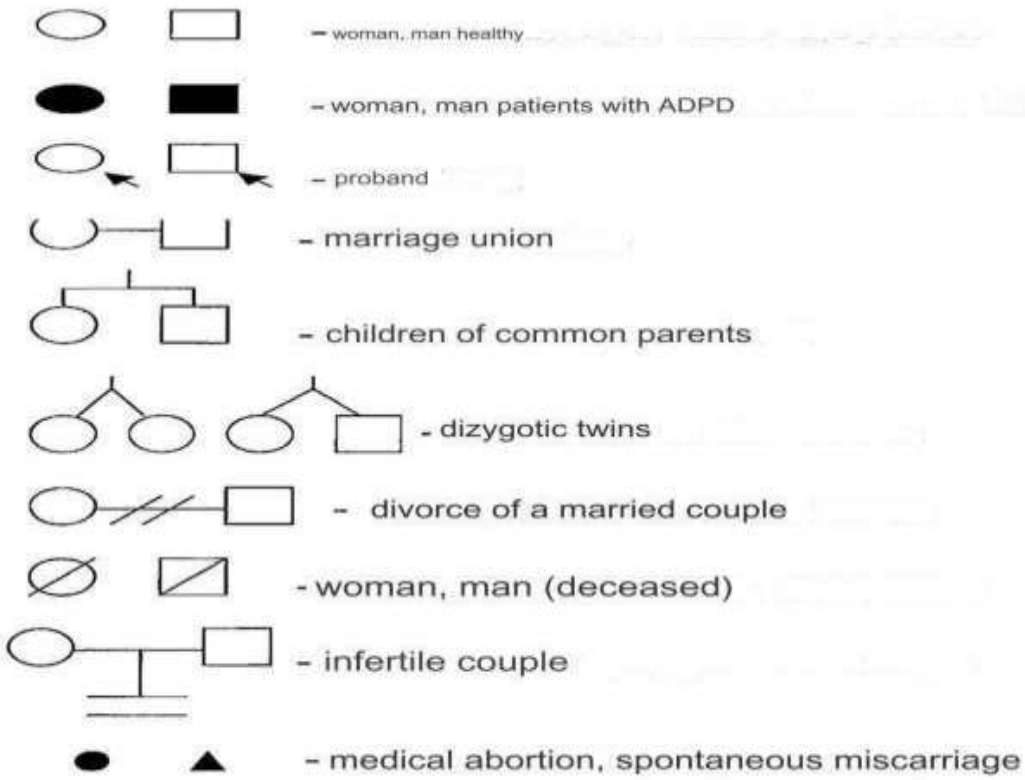
5. Stratification of the severity of CKD by stages, according to the modified National Kidney Foundation classification - K / DOQI (Table 2), coding according to ICD-10;

§2.2. Genealogical research method

The family history was collected by interviewing and personally examining the proband's family members of the first (parents, siblings) and second degree of kinship (grandmothers, grandfathers, aunts and uncles). Information about the health status of the proband's relatives was confirmed by the relevant medical documentation.

Graphic design of pedigrees was carried out using standard symbols and conventional designations [22,28] and was entered into the proband's examination card. Out of 60 families, 6 received information about relatives of 5 generations, 43 families - 4 generations, and 11 families - 3 generations. Symbols used in drawing up pedigree charts:

Each graphic representation of a fragment of the family tree was accompanied by a “legend,” which noted information about family members obtained during questioning, examination, and survey, and the symbols used in the diagram.



Pedigree analysis allowed us to assume the type of inheritance of the disease. Autosomal dominant inheritance was confirmed in the presence of signs of the disease in relatives of both sexes of the first and/or second degree of kinship. In the absence of kidney cysts in relatives, the diagnosis was interpreted as polycystic kidney disease of unspecified inheritance type.

§2.3. Evaluation of the functional state of the kidneys

Renal function was assessed by determining the SCF (by endogenous creatinine clearance and the Schwartz calculation formula), by the Zimnitsky test, and the acid- base balance of the blood. The stage of chronic kidney disease (CKD) was determined based on the SCF data obtained.

SCF was determined by the clearance of endogenous creatinine (Rehberg-Tareev test) and calculated using the Schwartz formula.

Normal values of SCF in children and adolescents according to the National Kidney Foundation - K / DOQI are presented in Table 6

Table 6

Normal SCF values in children and adolescents

(filed by National Kidney Foudation - K / DOQI [16,18]

Age(gender)	Mean GFR ± SD (ml/min/1.73 *mg g)**
1 week (premature boys) and girls)	15.3 ±5.6
2-8 weeks (premature boys and girls)	28.7 ±13.8
>8 weeks (premature boys and girls)	51.4
1 week (full-term boys and girls)	40.6 ± 14.8
2-8 weeks (full-term boys) and girls)	65.8 ± 24.8
>8 weeks (full-term boys) and girls)	95.7 ±21.7
2-12 years (boys and girls)	133.0 ±27.0

SD * - standard deviation.

The average daily clearance of endogenous creatinine was determined by collecting urine over the course of the day, and a single determination of plasma creatinine during the day (Rehberg-Tareev test). The absolute clearance of endogenous creatinine was calculated using the formula:

Cer = Ucr / Pcr * V

Where Ccg is the clearance of endogenous creatinine in ml/min, U cg is the concentration of creatinine in urine, Per is the concentration of creatinine in plasma, V is the minute diuresis in ml/min.

Relative creatinine clearance was calculated by converting the absolute value to the standard body surface area of an adult and the body surface area of a child, formula:

Rel Ssg = $\frac{\text{Abs Ssg x 1.73m}^2}{\text{Baby's body surface}}$,

Where Rel Ccg is the relative creatinine clearance, Abs Ccg is the absolute

Endogenous creatinine clearance, 1.73m2 - standard body surface area of an

adult.

Tables 7 and 8 present normal values of creatinine in blood and urine.

Table 7

Normal values of creatinine in blood and urine [11,19]

Age (years)	Blood creatinine		Urine creatinine	
	µmol/l	mg/dl	µmol/kg/d	mg/kg/day
<2	35-40	0.4-0.5	62-88	7.1-9.9
2-8	40-60	0.5-0.7	108-188	12.2-21.2
9-18	50-80	0.6-0.9	132-212	14.9-23.9

Table 8

Normal values of creatinine in urine [8]

	Adults	children
creatinine (mmol/day)	8.8-17.7	2.5-15

Normal values of SCF measured by endogenous creatinine clearance are presented in Table 9.

Table 9

Normal values of glomerular filtration rate (GFR) measured by endogenous creatinine clearance [13]

	Novorozh daily	1-2 weeks	6-12 months	1-3 years	adults
GFR [1] ml/min x 1.73 m^2	26±2	54±8	77±14	9b±22	118±18

Mean ± standard error of the mean

Glomerular hyperfiltration was defined as a glomerular filtration rate >140 ml/min/1.73 m^2, calculated based on endogenous creatinine clearance [52,53].

The percentage of tubular water reabsorption was calculated using the formula:

$$PB = \frac{(Rel\ Ccr - V) \times 100\%}{}$$

Rel Ssg

Where RV is tubular reabsorption of water (%), Rel Ccr is relative creatinine clearance (ml/min), V is minute diuresis (ml/min).

Normally, tubular reabsorption is 98-99%, to determine the SCF, the Schwartz formula was used for children and adolescents under 18 years of age [31]: SCF (ml/min/ 1.73 m^2) = K xHt ÷ Per,

Where Per is serum creatinine (mg/dl), Ht is height (cm), K is the coefficient established by regression analysis, the values of which in different age categories are presented in Table 10.

Table 10

Values of the coefficient in the Schwartz formula [21]

	Coefficient (whencreatinine is expressed in mg/dl)	Coefficient (when creatinine is expressed in mmol/l)
birth weight infants <1 year	0.33	29.2
normal birth weight babies < 1 year	0.45	39.8
children from 2 to 12 years old	0.55	48.6
female adolescents aged 13 to 18 years	0.55	48.6
male adolescents aged 13 to 18 years	0.7	61.9

Chronic kidney disease (CKD) should be understood as the presence of any signs of kidney damage that persist for three months or more, regardless of the nosological diagnosis [14].

The diagnosis of CKD is established based on the following criteria:

1. The presence of any clinical markers of kidney damage, including changes in the composition of urine and blood, confirmed at an interval of at least 3 months;

2. Any markers of irreversible structural changes in an organ, identified once during an intravital morphological examination of the organ or during its

visualization;

3. A decrease in the glomerular filtration rate of <60 ml/min/1.73 m", for three or more months, regardless of the presence of other signs of kidney damage.

The stage of CKD in patients was determined according to the modified National Kidney Foundation classification - K / DOQI (Table 11).

Table 11

Stratification of CKD stages by SCF level [40,41,46]

Stage of CKD	**Description**	**SCF (ml/min/ $^{1.73m2}$)**
I	Renal injury with optimal or increased GFR	>90
II	Renal injury with mild reduction in GFR	60-89
SHA	Renal injury with moderate reduction in GFR	45-59
IIIB	Renal injury with significant reduction in GFR	30-44
IV	Renal injury with severe decline in GFR	15-29
V	Terminal renal failure	<15

The coding of the stages of chronic kidney disease according to ICD-10 (as amended in October 2007) was carried out in accordance with Table 12.

Table 12

Correspondence of CKD stages to ICD-10 coding [17,38]

Stage of CKD	ICD-10 code
I	N 18.1
II	N 18.2
III A	N 18.3
III B	
IV	N 18.4
V	N18.5

§2.4. Blood pressure assessment

Blood pressure in all patients was measured using the Korotkov method. In children and adolescents, the assessment was carried out using special tables of the dependence of blood pressure on age, gender and height. Arterial hypertension (AH) was diagnosed when an increase in systolic and/or diastolic blood pressure

above the 95th percentile was recorded based on the results of three-time blood pressure measurements [47]. In adult patients, AP was assessed according to the 2007 recommendations of the European Association of Cardiologists [50].

§2.5. Method for assessing survival of patients with autosomal dominant polycystic kidney disease

The method of survival assessment involves the use of life table construction (table 13) and the non-interval method of Kaplan E. L., Meier P. (1958) [39]. The term "survivors" refers to patients with ADPKD who survived to the end of observation, have normal renal function or compensated renal failure that does not require renal replacement therapy.

Table 13 Life table [12]

T0	*T l,*	***N k***	***p k***	*SCH*	***N k -n***	***Rk***	*Ilk, %*
1							
2							
3							
4							
5							
6							
7							

Note: the *t k values* in brackets contain the duration of observation of surviving patients.

The result of the calculation is the probabilities lt 1, *lt (10* and lt *]4.*

The following notations are introduced in the table:

k - time interval number 4;

tk - duration of the patient observation time interval (the beginning of all intervals coincides with the beginning of the time count), years;

N k - the number of observed patients at the end of the (J-1) th interval;

p k - the number of patients with a fatal outcome or the development of ESRD in the time interval from *tk -1* to *tk*;

w k - the number of patients whose examination was not carried out in the time interval from *tk -1* to *tk,* and in all subsequent observation intervals;

(*N k — n k — w k*) is the number of observed patients at the end of the interval tk;

$$-\frac{\text{Pk Nk-nk-Wk}}{\text{1+N-n-W =}}-$$ – conditional probability of patient survival

on the time interval from tk-1 to tk;

11k is the probability (unconditional) of the patient's survival at time tk.

Calculations of the probability of survival were carried out using the formula (Dvoyrin VV, Klimenkov AA, 1985)

$$l_{tk} = \prod_{i=1}^{k}\left(\frac{N_i - n_i - w_i}{1 + N_i - n_i - w_i}\right),$$

where only numbers corresponding to fatal outcomes and development of ESRD are taken as index i. In our table, i = 1 is taken to calculate 11; i = 1 and 10 are taken to calculate 1110; i = 1, 10 and 14 are taken to calculate 1,14.

For the probability values we found 11, 110 and 114, according to the formula:

$$m_{tk} = l_{tk}\sqrt{\sum_{i=1}^{k}[(N_i - n_i - w_i)(1 + N_i - n_i - w_i)]^{-1}}$$

the corresponding values of the average errors *mt 1, mt 10* and *t t 1 4 are calculated* (for the index / the above rules also apply here).

§2.6. Methods of statistical processing of research results

The reliability of differences in the compared parameters was determined using the parametric Student's t- test and the nonparametric Mann-Whitney U -test. The critical level of reliability of the null statistical hypothesis (p) was taken as 0.05. Differences in the compared parameters were considered reliable at $p<0.05$ [52]. The least squares method was used to calculate the linear regression function [5].

CHAPTER III. RESULTS OF THE GENEALOGICAL STUDY OF 60 FAMILIES WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

In a study of 79 families, the diagnosis of polycystic kidney disease was confirmed in 133 members of 71 families: 78 children and adolescents (probands) aged 3 months to 18 years and 55 adults (parents) aged 30 to 55 years.

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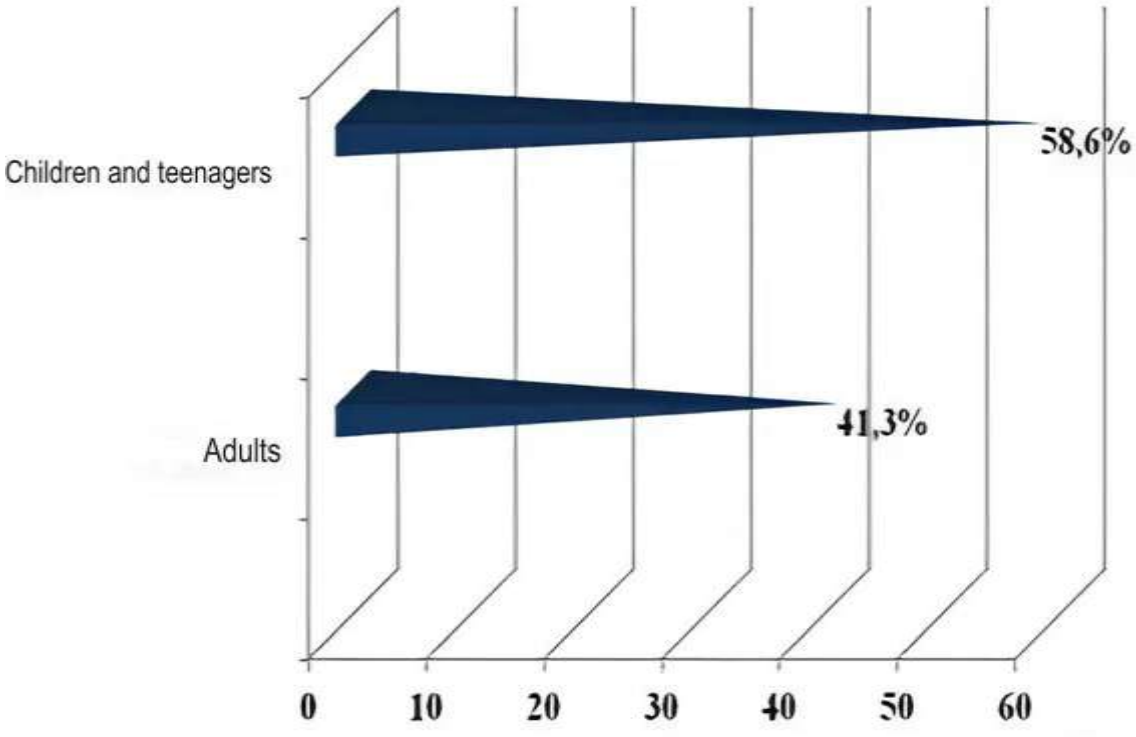


Figure 4. Confirmation of the diagnosis of polycystic kidney disease in patients

Autosomal dominant polycystic kidney disease was established when the disease was present in at least two generations: in relatives of both sexes of the 1st (parents, siblings) and/or 2nd degree (grandmothers, grandfathers, uncles, aunts) of kinship.

As a result of genealogical analysis of 71 families diagnosed with polycystic kidney disease, it was possible to identify 55 families (62 children and adolescents and 55 adults) with a clear autosomal dominant type of inheritance of polycystic kidney disease. The disease was inherited from the father by 33 probands, from the

mother by 29 probands.

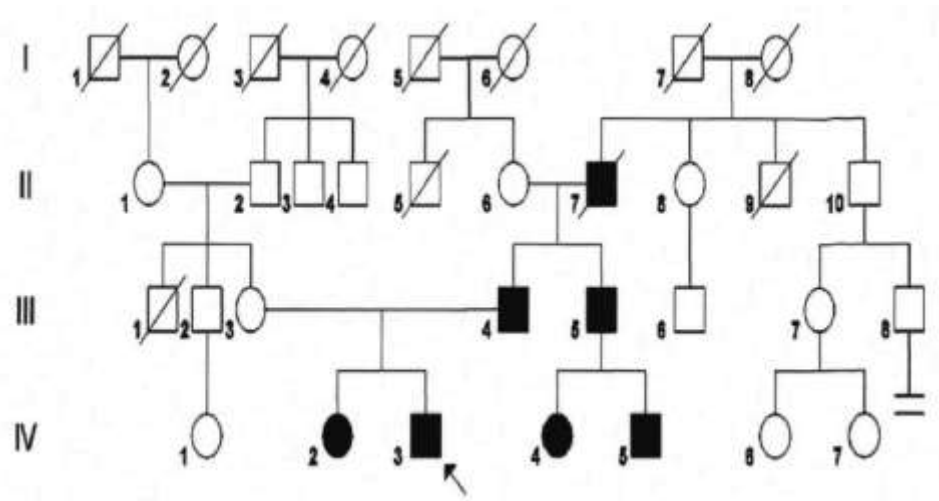


Figure 5. Fragment of the family tree of A. (07/22/1986)

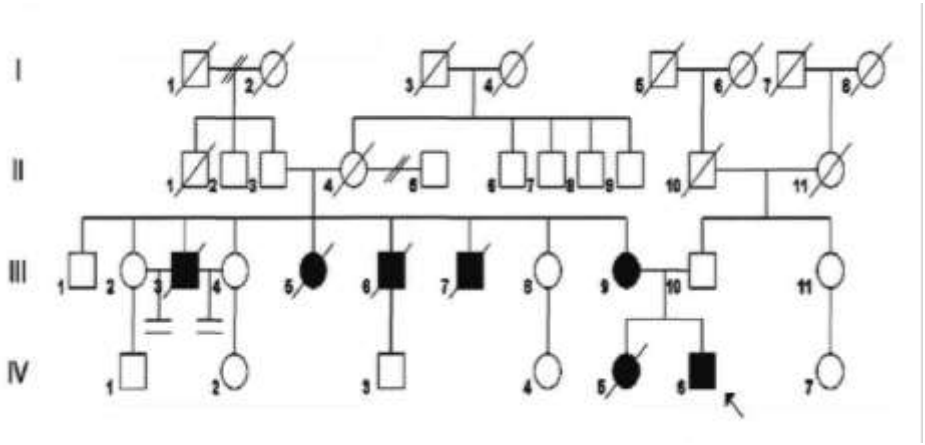


Figure 6. Fragment of the family tree of Ch. (09/08/1987)

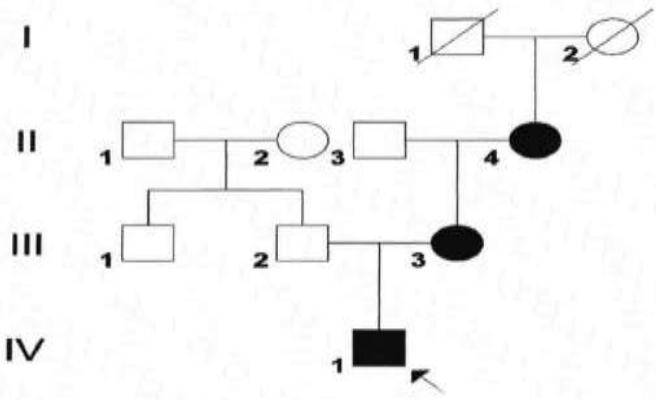


Figure 7. Fragment of the family tree of Ch. (07/22/1990)

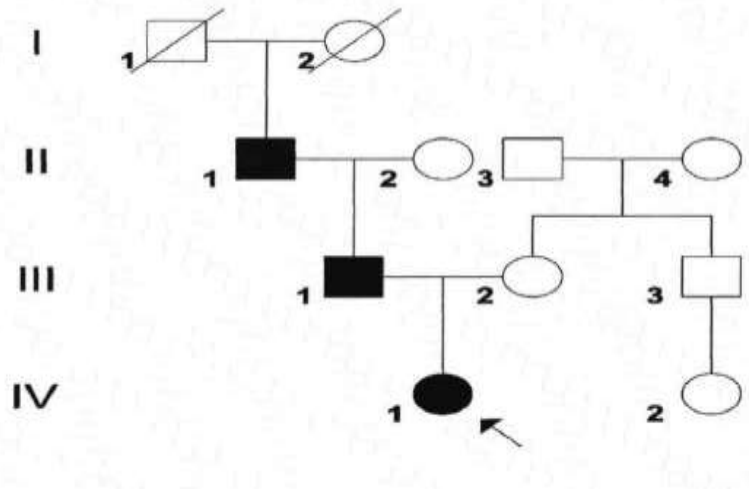


Figure 8. Fragment of the family tree of D. (09.12.1983)

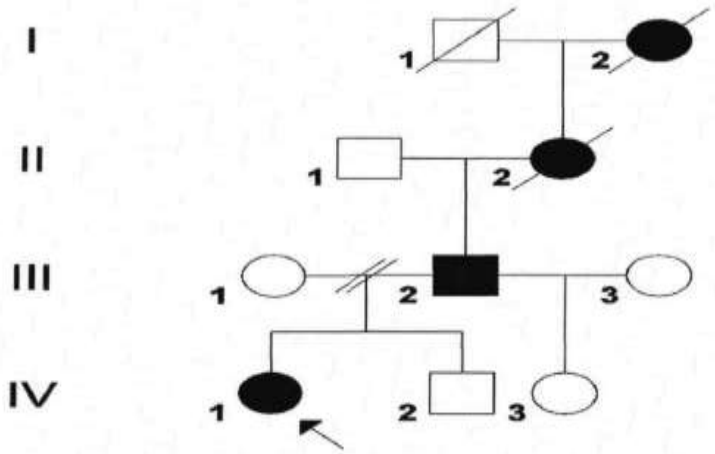


Figure 9. Fragment of the family tree of D. (04.02.1997)

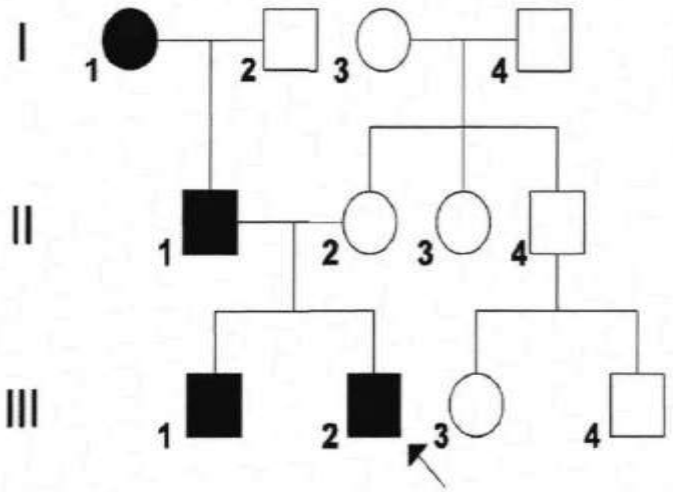


Figure 10. Fragment of the family tree of D. (07.06.1985 and 01.04.1987)

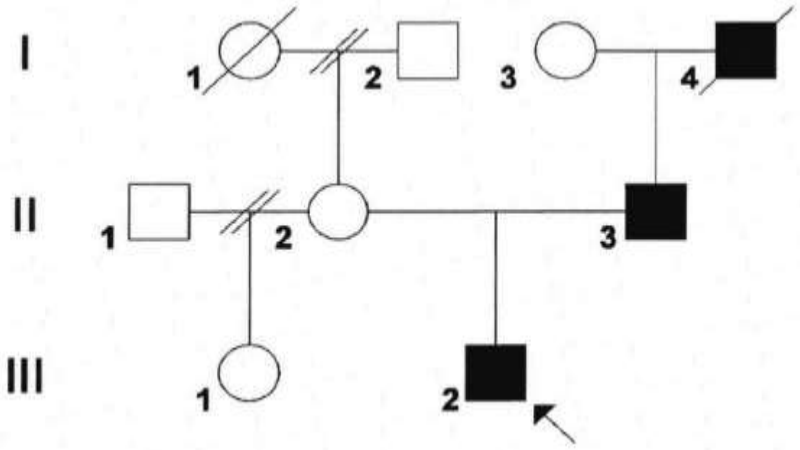


Figure 11. Fragment of the family tree of F. (05/25/1994)

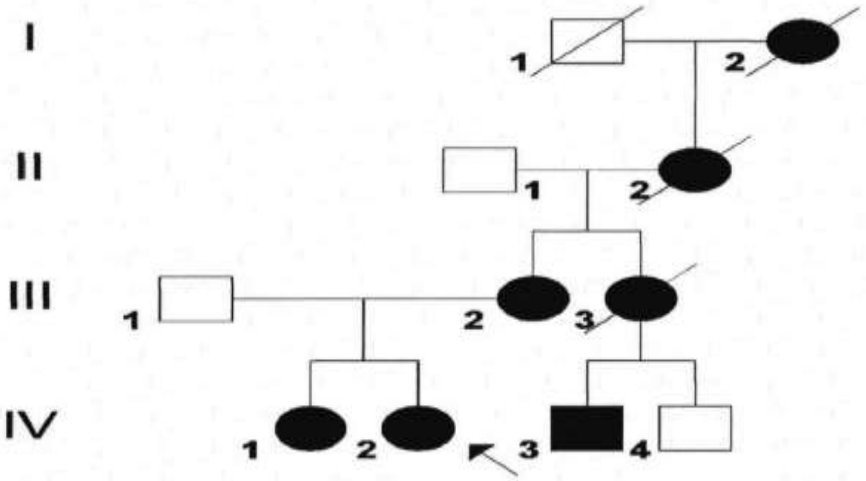


Figure 12. Fragment of the family tree of G. (10/02/1994)

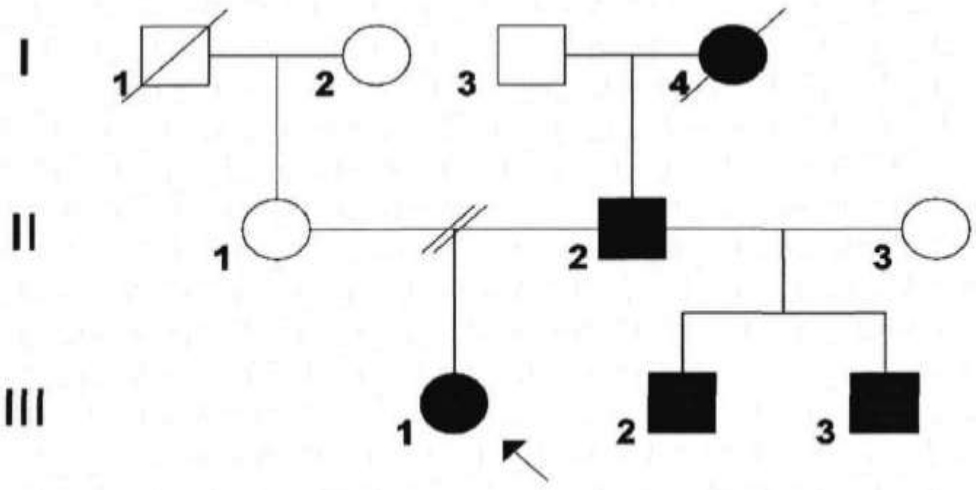


Figure 13. Fragment of the family tree of G. (03/14/1987)

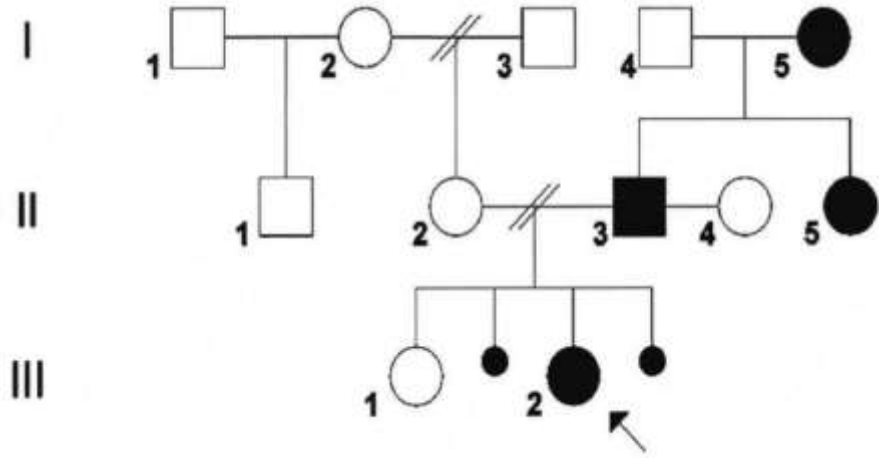


Figure 14. Fragment of the family tree of G. (02/25/2003)

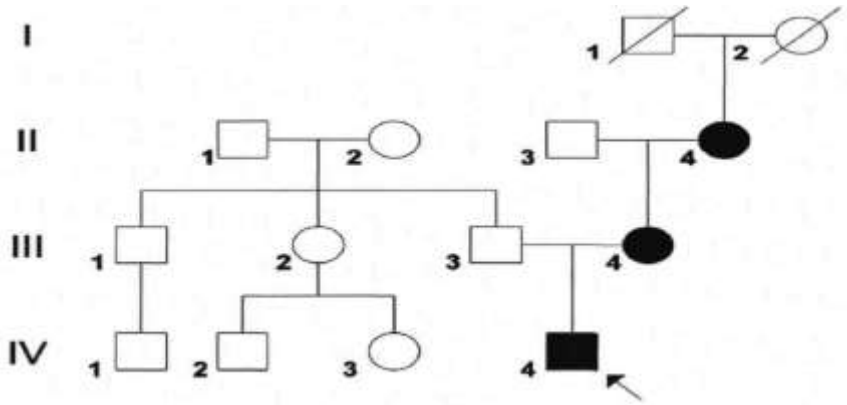


Figure 15. Fragment of the family tree of I. (01/07/1998)

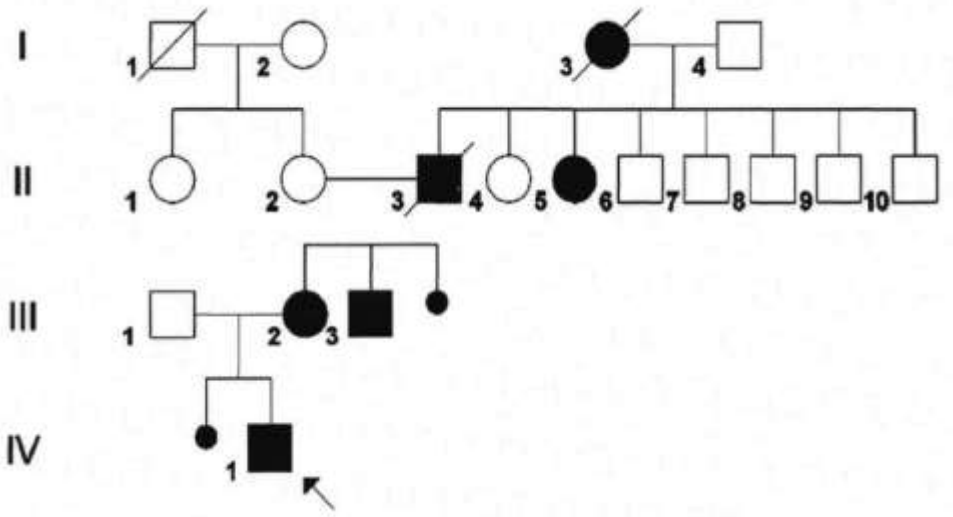


Figure 16. Fragment of the family tree of K. (01/24/2007)

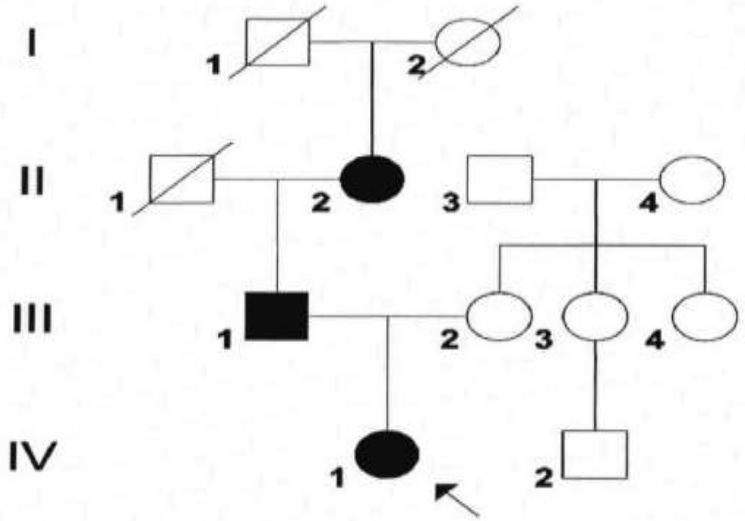


Figure 17. Fragment of the family tree of K. (03/14/1991)

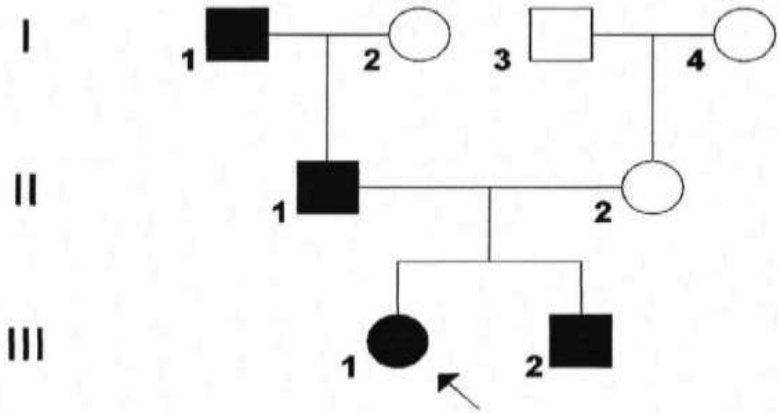


Figure 18. Fragment of the family tree of X. (09.08.1988 and 09.06.1994)

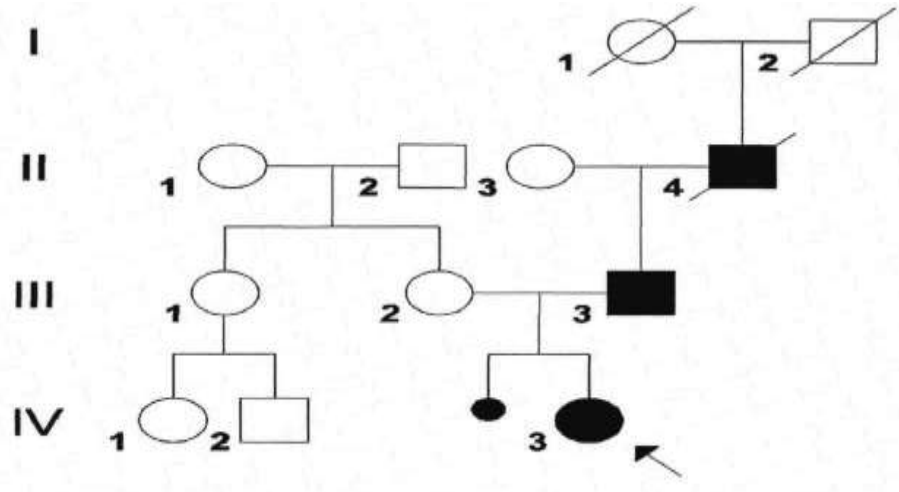


Figure 19. Fragment of the family tree of K. (07/07/1998)

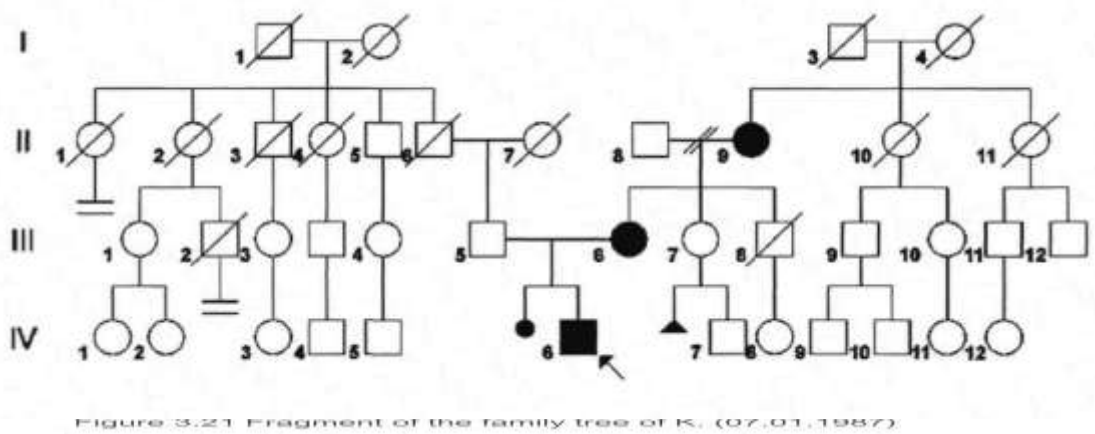


Figure 3.21 Fragment of the family tree of K. (07.01.1987)

Figure 20. Fragment of the family tree of K. (12/25/1987)

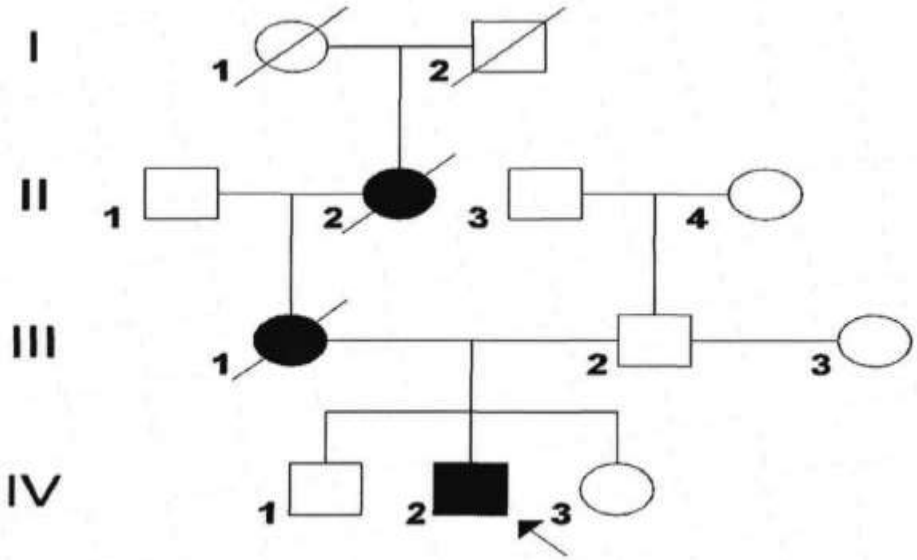
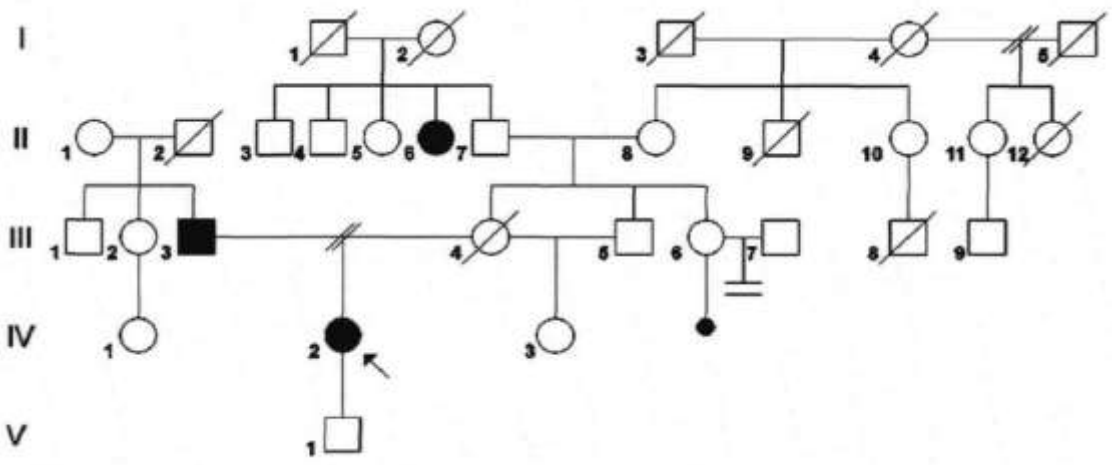


Figure 21. Fragment of the family tree of K. (19/02/1988)



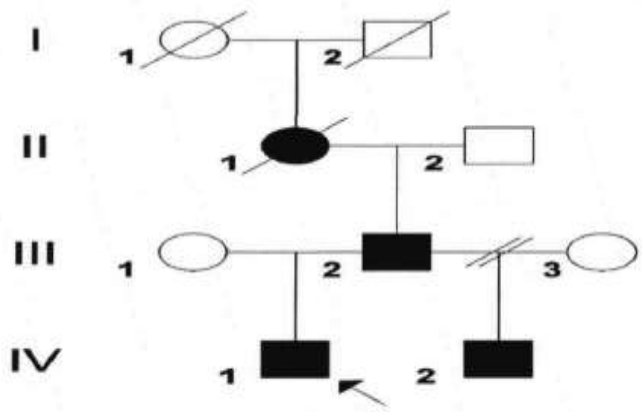


Figure 23. Fragment of the family tree of L. (09/18/1995)

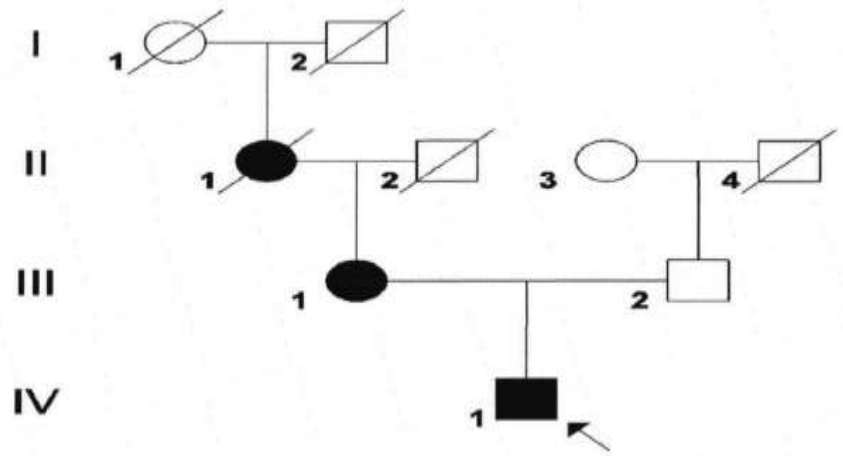


Figure 24. Fragment of the family tree of M. (01/29/1994)

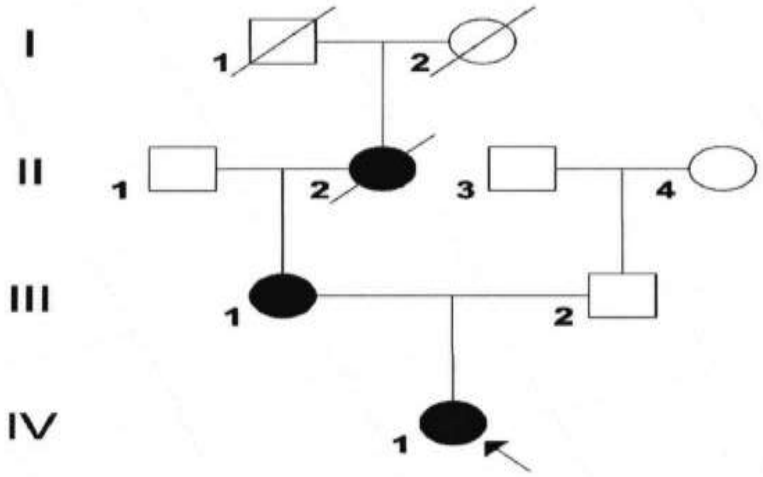


Figure 25. Fragment of the family tree of M. (07/28/1990)

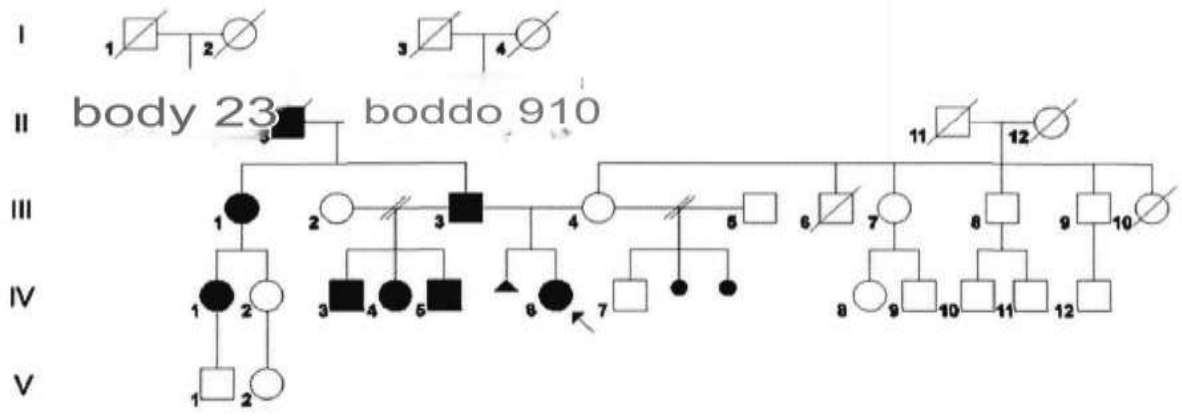


Figure 26. Fragment of the family tree of M. (09.20.1984: 11.22.1986: 06.03.1989: 07.31.1995)

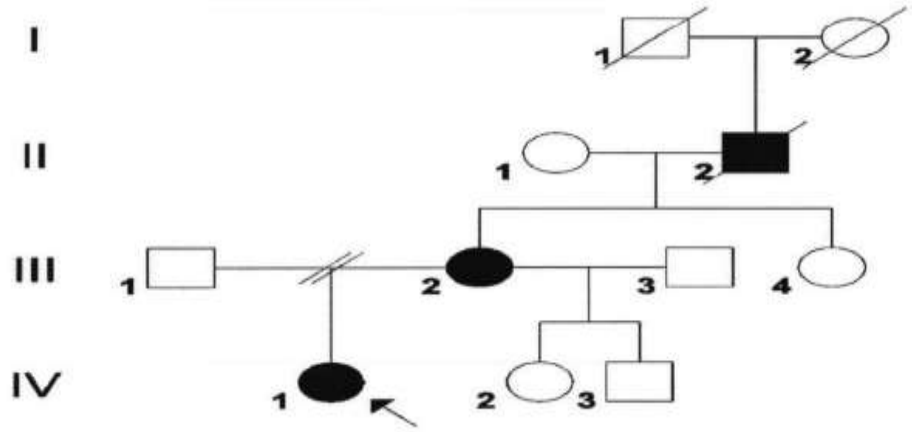


Figure 27. Fragment of the family tree of N. (18/04/1997)

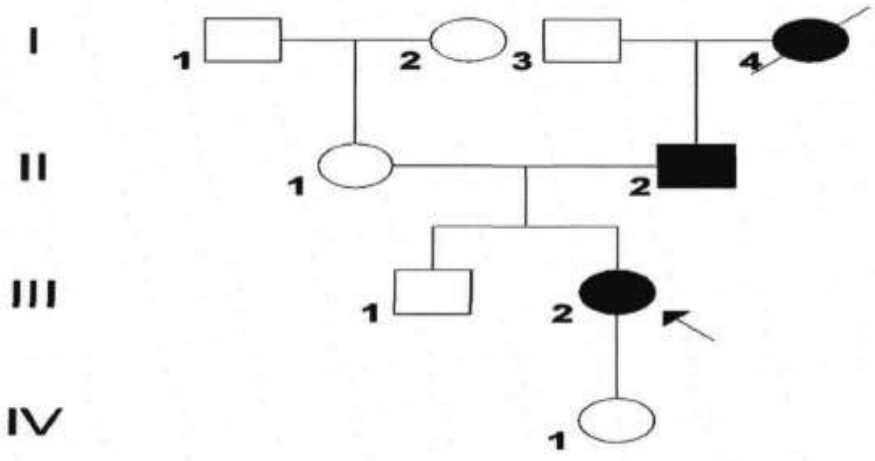


Figure 28. Fragment of the family tree of P. (01.01.1984)

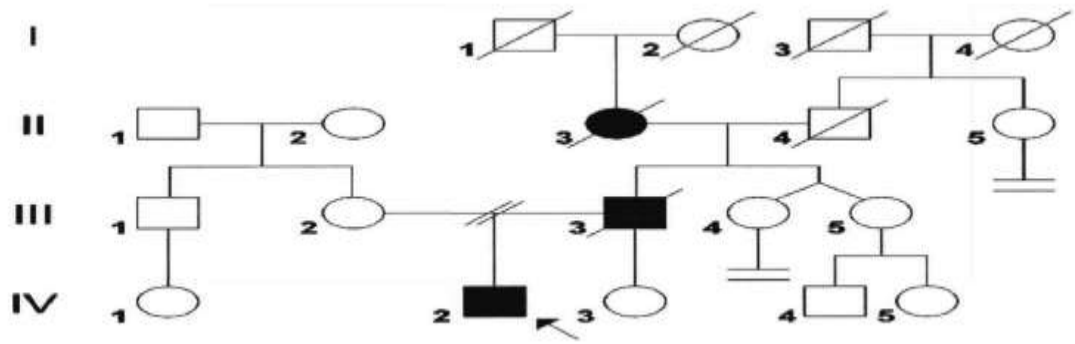


Figure 29. Fragment of the family tree of P. (06/20/1988)

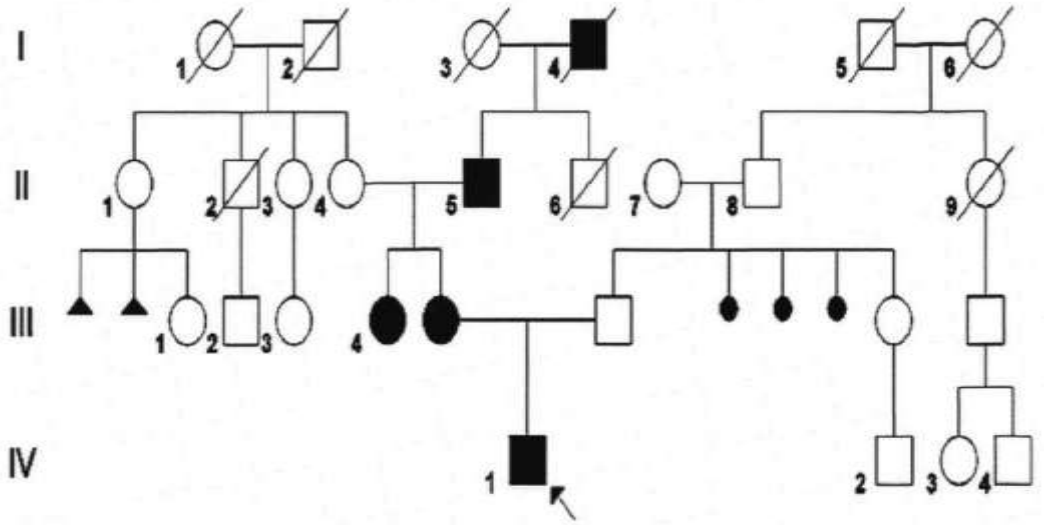


Figure 30. Fragment of the family tree of P. (12/24/2002)

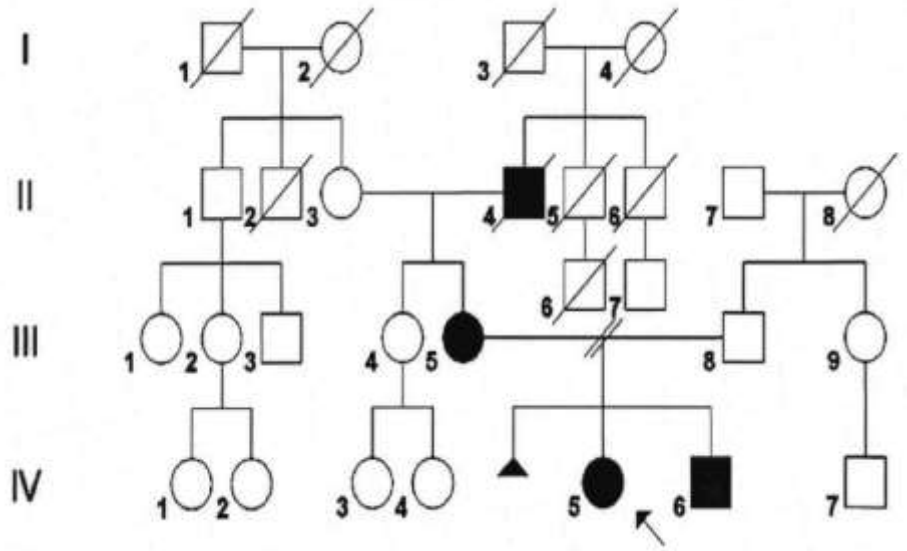


Figure 31. Fragment of the family tree of S. (10.08.1987 and 26.10.1989)

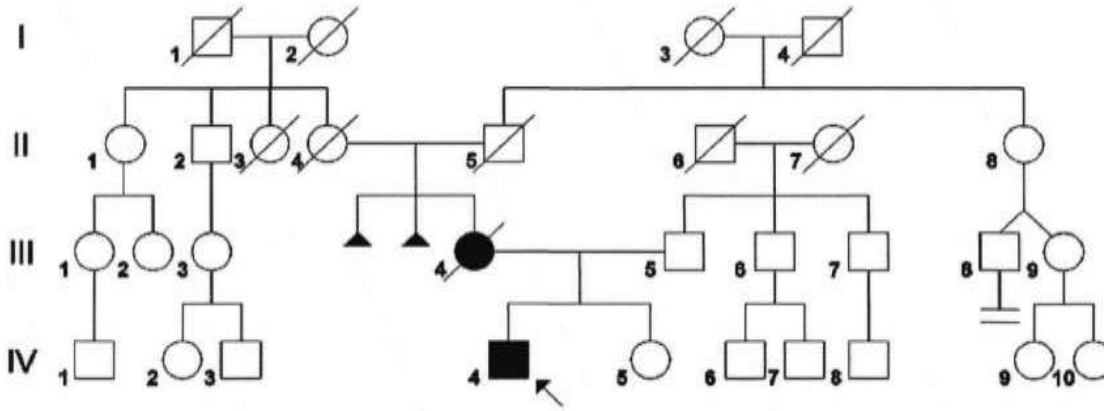


Figure 32. Fragment of the family tree of Sh. (08/20/1985)

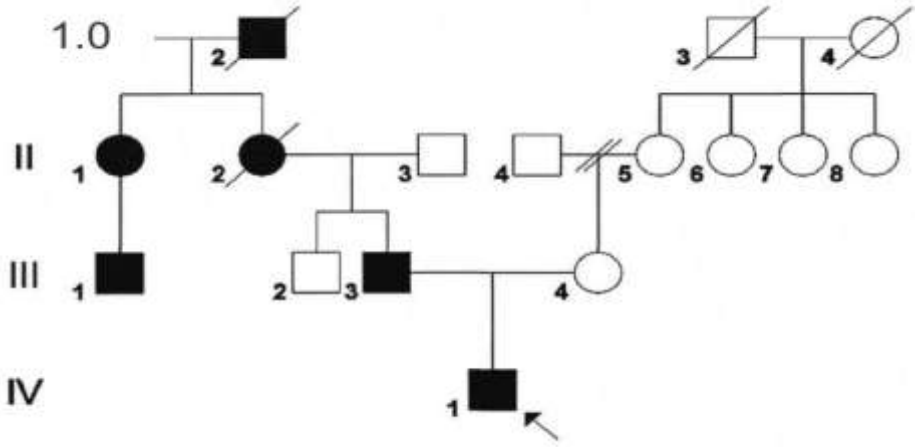


Figure 33. Fragment of the family tree of S. (04.04.2001)

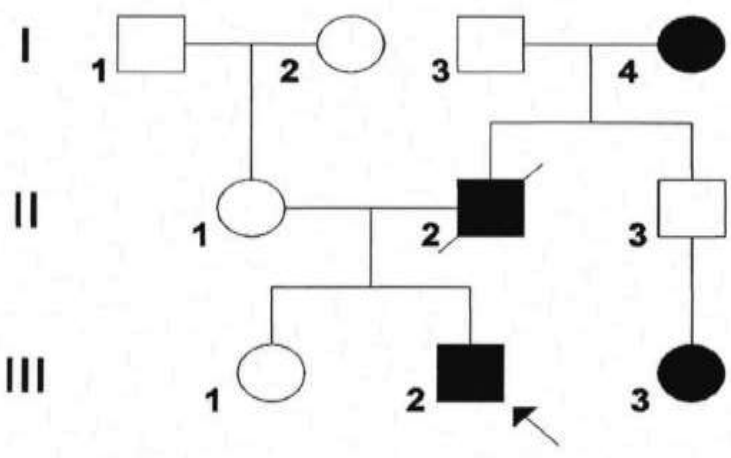


Figure 34. Fragment of the family tree of S. (09.22.1989)

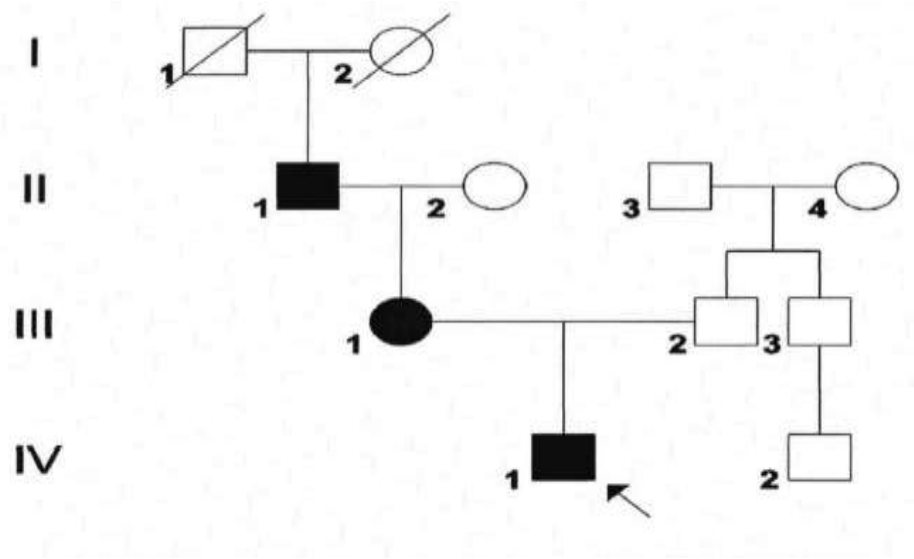


Figure 35. Fragment of the family tree of S. (11.05.2000)

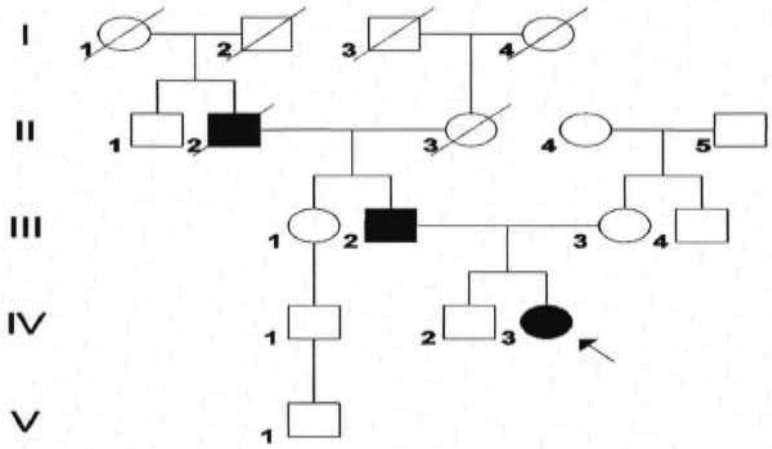


Figure 36. Fragment of the family tree of S. (05/23/2007)

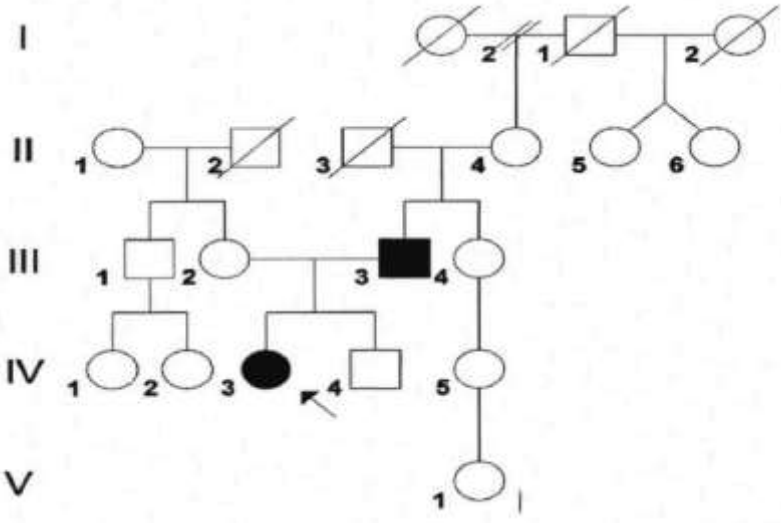


Figure 37. Fragment of the family tree of S. (10/20/1993)

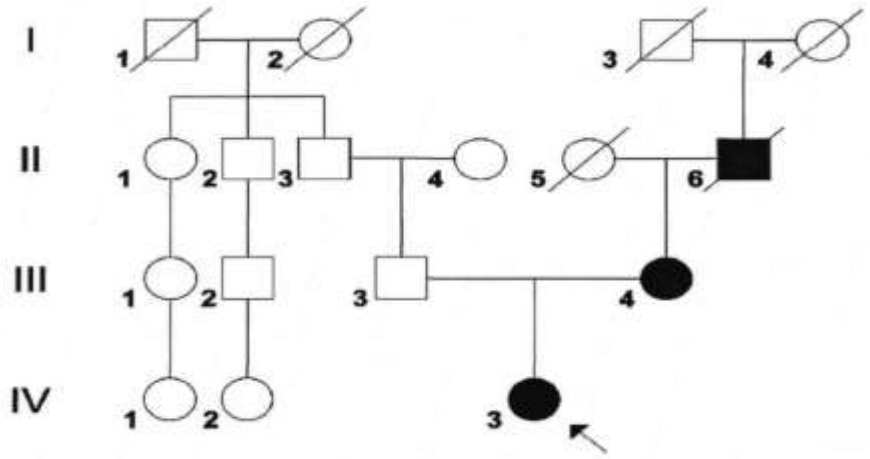


Figure 38. Fragment of the family tree of S. (10/27/1990)

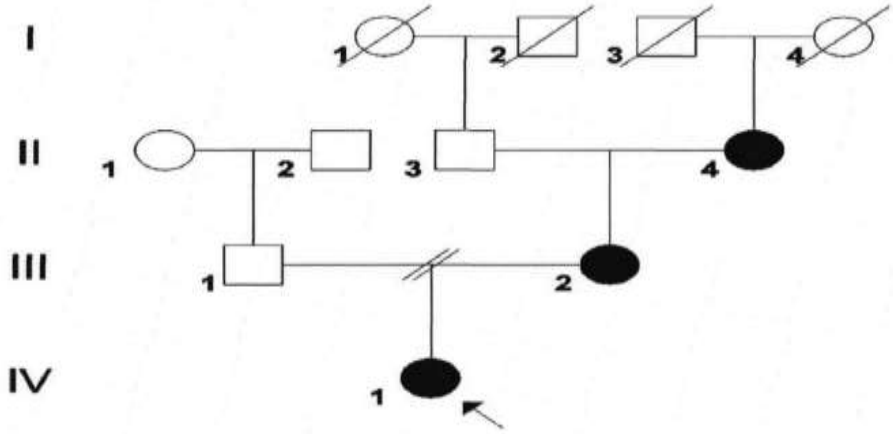


Figure 39. Fragment of the family tree of T. (05.11.1986)

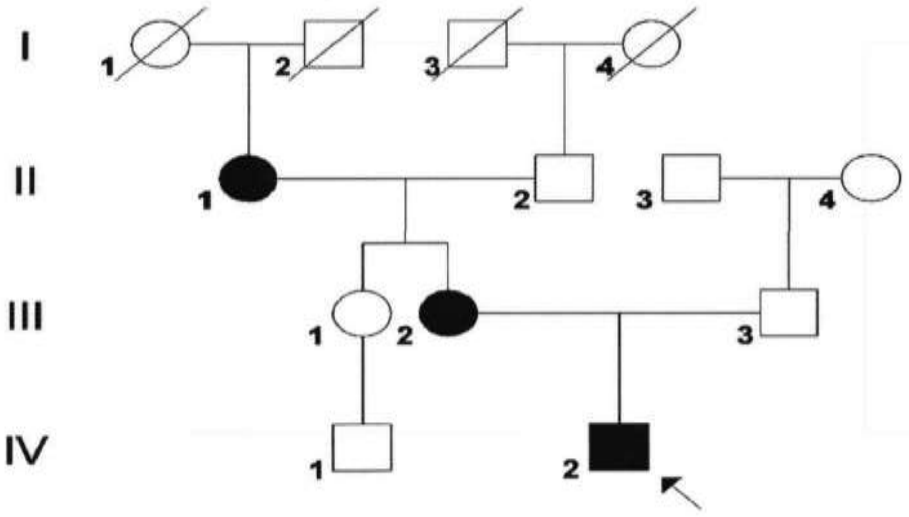


Figure 40. Fragment of the family tree of V. (01.15.1995)

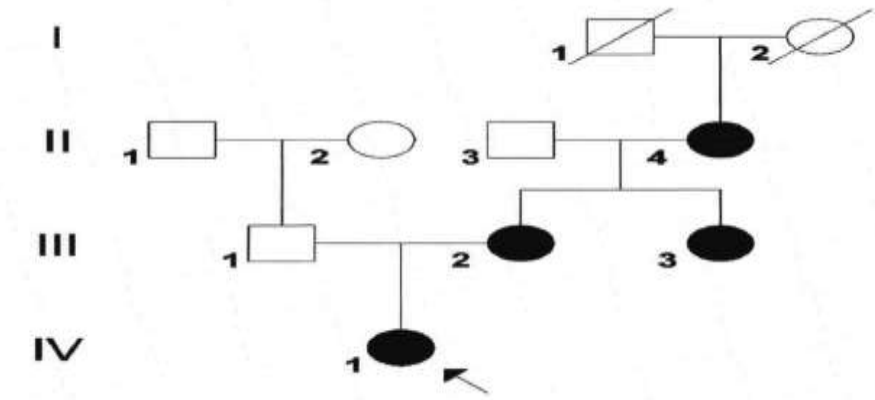


Figure 41. Fragment of the family tree of V. (08.02.2007)

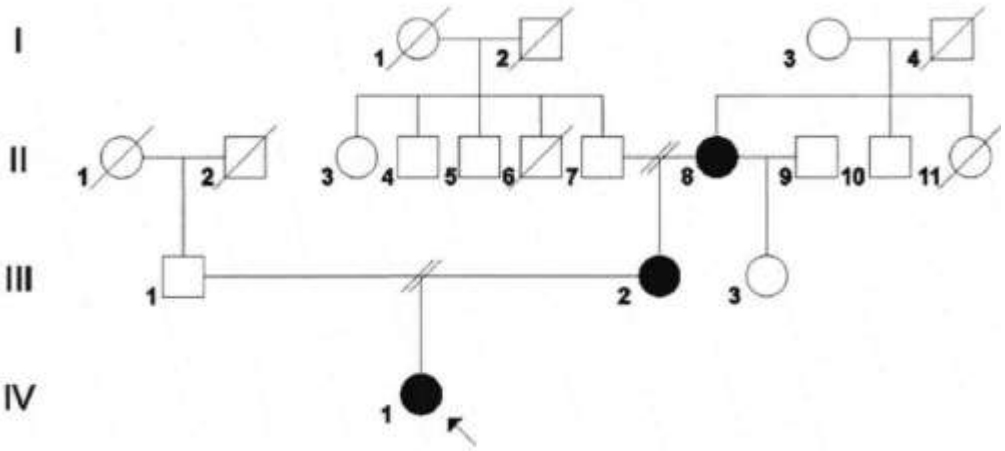


Figure 42. Fragment of the family tree of Z. (18.02.2005)

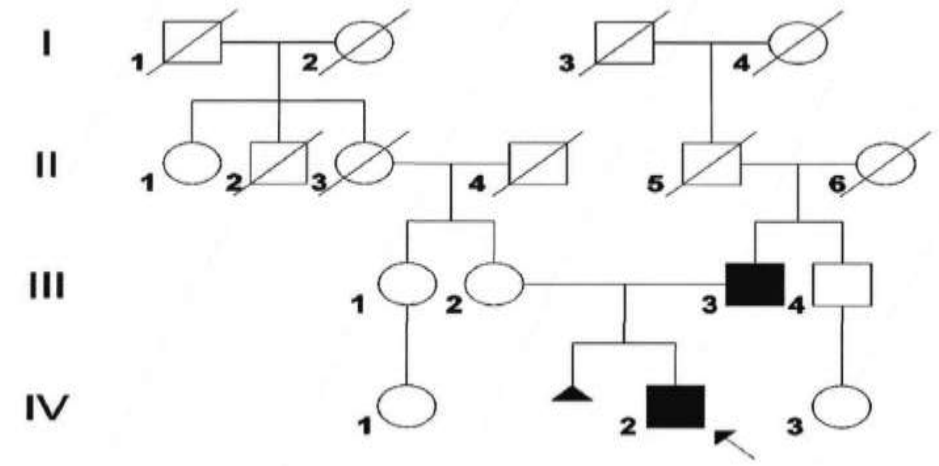


Figure 43. Fragment of the family tree of Z. (12/25/2000)

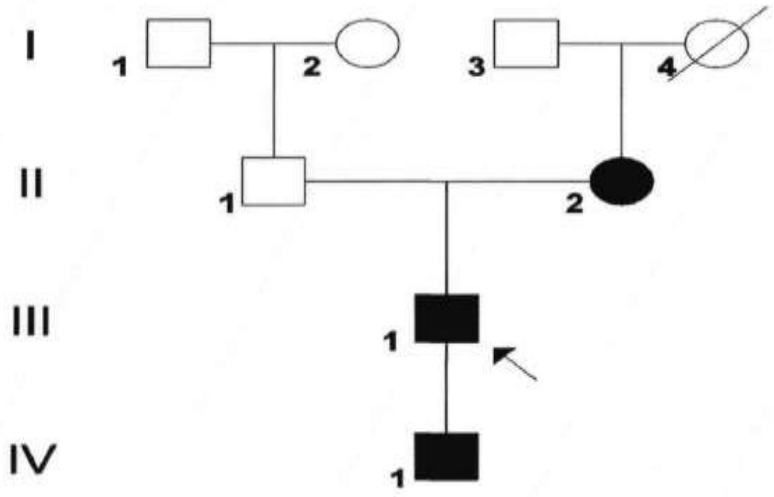


Figure 44. Fragment of the family tree of X. (06/09/1984)

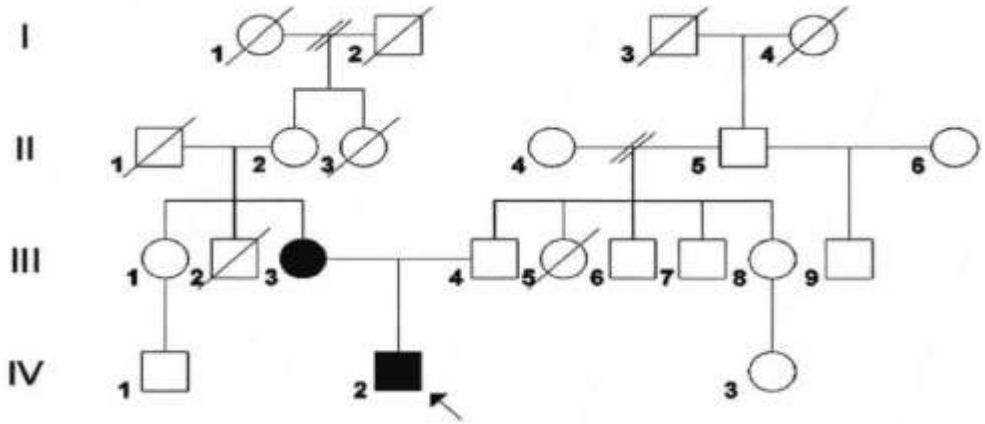


Figure 45. Fragment of the family tree of I. (06/25/1991)

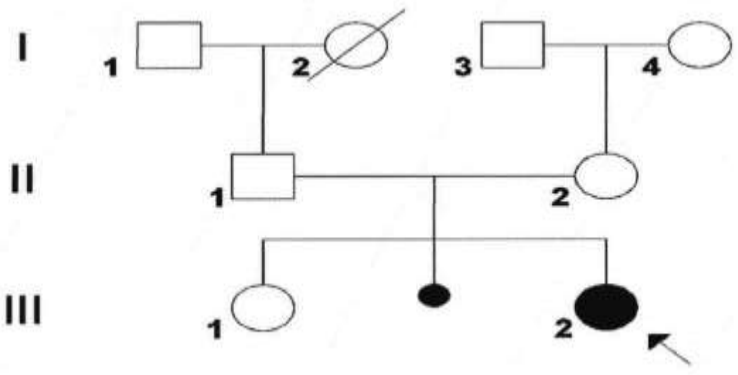


Figure 46. Fragment of the family tree of R. (12.10.1987)

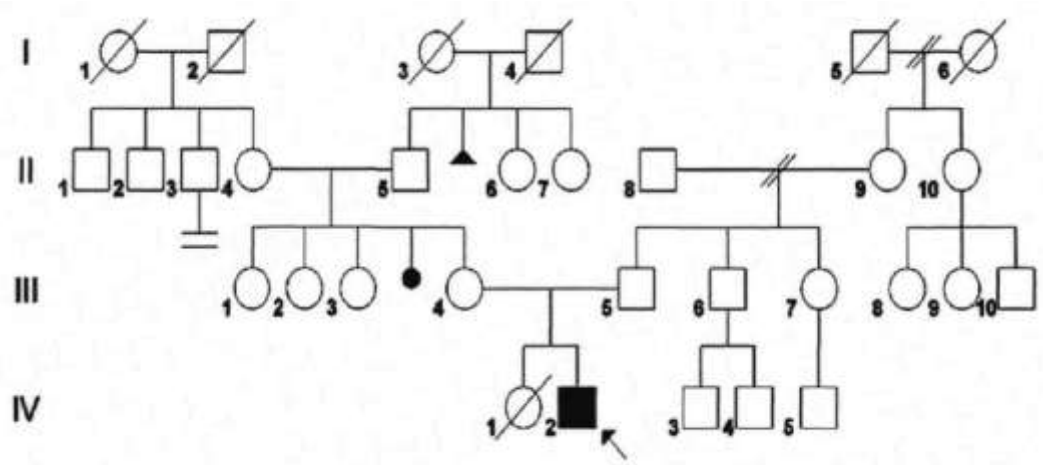


Figure 47. Fragment of the family tree of R. (10.05.1991)

In 16 families, it was not possible to clearly establish the type of inheritance due to the absence of the disease in relatives of the 1st and/or 2nd degree of kinship. In 5 of the 16 probands with an unspecified type of inheritance, due to the presence of bilateral multiple cysts (more than 6) in the kidneys, the presence of a denovo mutation was assumed and they were included in the main study group.

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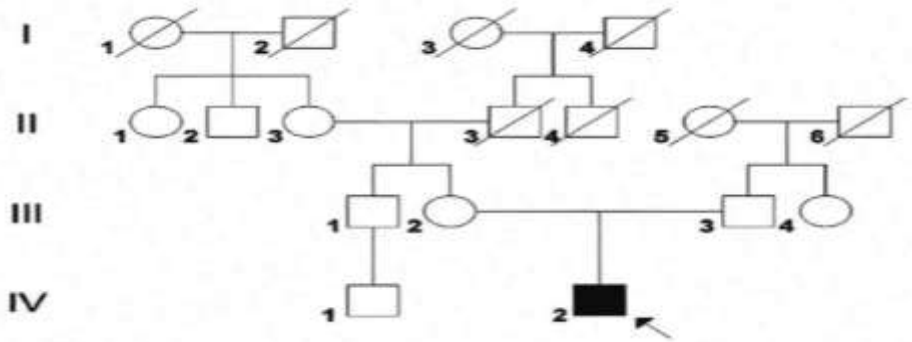


Figure 48. Fragment of the family tree of S. (18.08.2005)

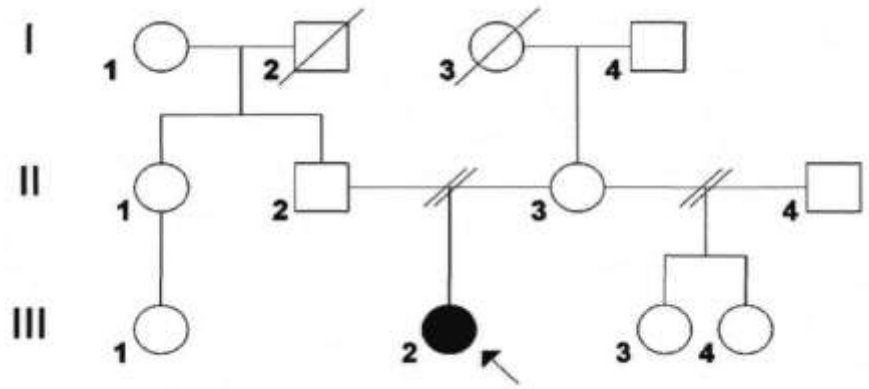


Figure 49. Fragment of the family tree of K. (20.07.1994)

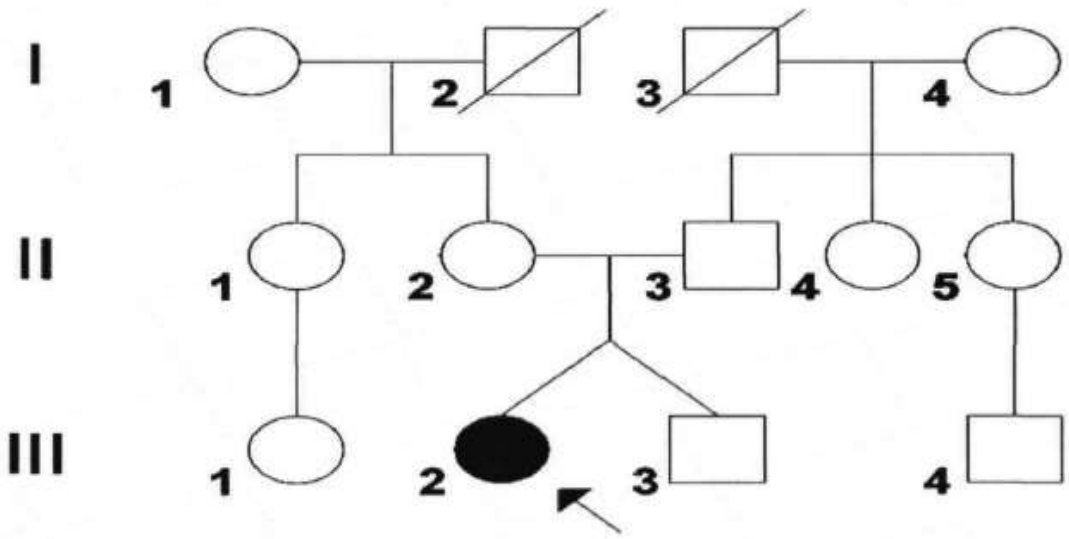


Figure 50. Fragment of the family tree of Z. (02.02.1995)

Thus, the study included 122 members (67 children and adolescents and 55 adults) of 60 families with autosomal dominant polycystic kidney disease. Among the children and adolescents (probands) were 36 boys and 31 girls aged from 3 months to 18 years. Among the adults (parents) were 27 men and 28 women aged from 30 to 55 years.

In 60 families, the disease manifested itself in 67 examined probands aged from 3 months to 18 years and 55 parents aged from 30 to 55 years (8 died). According to the pedigrees, autosomal dominant polycystic kidney disease was diagnosed in 10 siblings and 86 relatives of the 2nd to 4th degree of kinship. Four probands gave birth to children (aged from 1 to 4 years), 2 of whom (a boy and a girl) were diagnosed with ADPKD, and 2 (a boy and a girl) had no kidney cysts at the time of follow-up. Thus, in 60 families, 220 members are known to have been diagnosed with autosomal dominant polycystic kidney disease, including 118 women and 102 men (sex ratio 1.16:1).

CHAPTER IV. FUNCTIONAL STATE OF THE KIDNEYS AND STAGES OF CHRONIC KIDNEY DISEASE IN CHILDREN WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Features of diagnosis and course of autosomal-dominant polycystic kidney disease in 67 patients from 60 families

§4.1. Clinical characteristics of children with autosomal dominant polycystic kidney disease

A total of 67 children and adolescents **(**from 60 families) with autosomal dominant polycystic kidney disease (ADPKD) were examined, including 36 boys (53.7%) and 31 girls (46.3%), the ratio being 1.16:1.

The average age of children with ADPKD at the time of first detection of kidney cysts was 8.24±0.64 years, maximum 16.58 years, minimum 1 month. The average age at the time of diagnosis of polycystic kidney disease was 9.52±0.65 years.

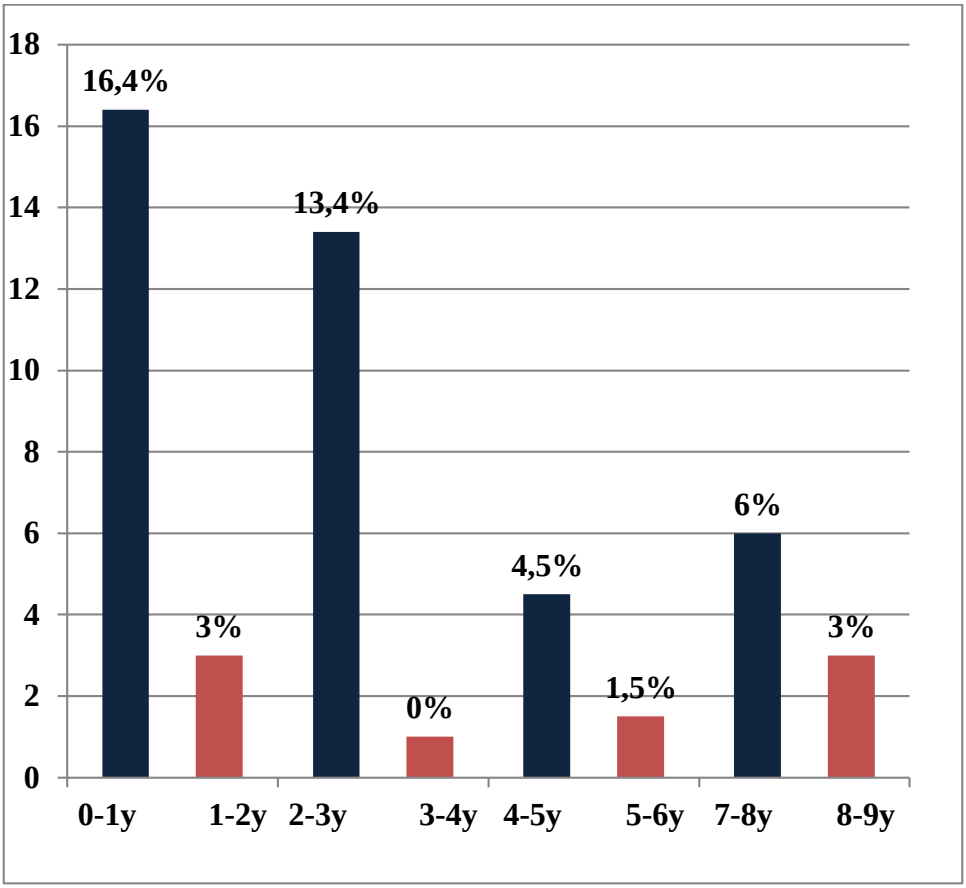
Table 14 shows that in 91% of cases in children and adolescents, cysts were first detected before the age of 15, of which 19.4% were detected before 18 months (very early detection), and 71.6% were detected from 19 months to 15 years.

Table 14

Age-related features of ultrasound diagnostics of renal cysts in 67 children and adolescents with ADPKD

Age	<18 months (very early detection)	19 months - 15 years	15 years 1 month - 18 years
Number of patients (%)	13 (19.4%)	48(71.6%)	6 (9%)

The distribution of children with ADPKD by age at the time of first detection of cysts is shown in figure*



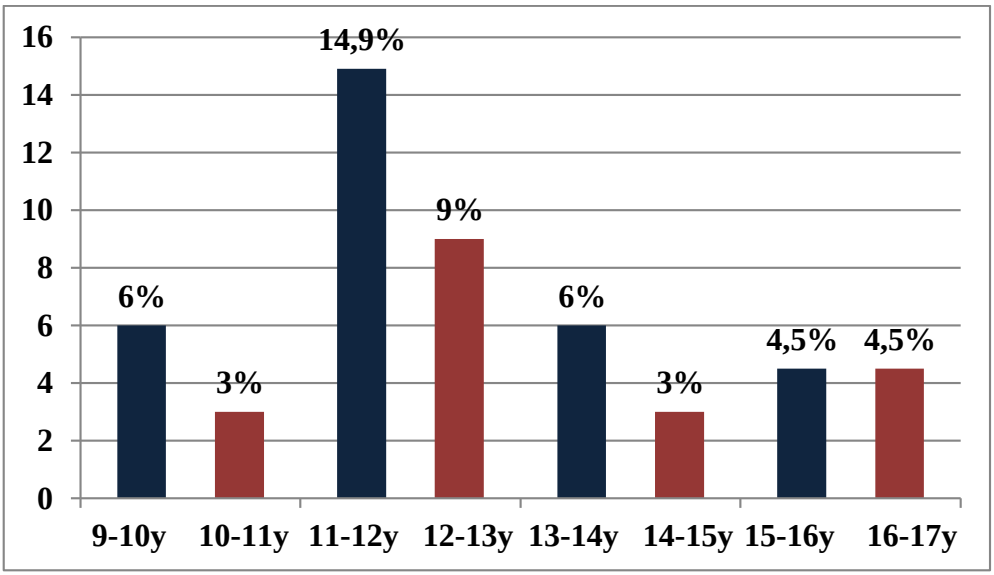


Figure50* Distribution of children with ADPKD by age at the time of first detection of cysts.

Of the 67 children and adolescents, 5 (7.4%) had no adverse family history, but given that ultrasound showed 5 or more cysts in the kidneys, it is assumed that they had a denovo mutation. This is consistent with the literature on ADTTGT, according to which denovo mutations account for 4-10% (Torres V. E., Harris P. C., 2007; Woryniec W., Jankowska M. M., Krol Eetal., 2008; Reed B., McFann K., Kimberling W. Jetal., 2008; Mekahli D., Woolf A. S., Bockenhauer D., 2010).

By the time of the first detection of kidney cysts, 50 of 62 probands with ADPKD had information about an aggravated family history. The parents of 12 probands (11 families) learned about the disease only after examination, due to the detection of kidney cysts in children. The age of detection of cysts in 55 adults ranged from 17 to 53 years, on average 29.4±1.3 years. The disease was inherited from the father in 33 probands, from the mother - 29 probands.

The structure of reasons for which an ultrasound examination was performed that revealed cysts in the kidneys is presented in Table 15.

Table 15

Reasons for performing ultrasound examination in 67 probands with ADPKD

Reasons	Burdened Inheritance of veins Nost	Pain in stomach/ lower back/ side	Other nephrolo - gic pathology	Diseases others organs and systems	Antenna - tal noe suspicion
Quantity children	22	12	14	14	5
%	32.8	17.9	20.8	20.8	7.7

Table 16 presents the combined pathology in 67 children with autosomal dominant polycystic kidney disease.

Table 16

Combined pathology in 67 children and adolescents with ADPKD

Pathology	Quantity children	%
Pathology of the urinary system (chronic pyelonephritis and interstitial nephritis, glomerulonephritis, cystitis, neurogenic bladder dysfunction, enuresis, hypospadias, meatostenosis, hydronephrosis, VUR, incomplete duplication of the kidneys, nephroptosis)	48	71.6
Pathology of the skeletal system (postural disorders, chest deformities, flat feet, sandal gap, hip dysplasia, gothic palate, Kimmerle anomaly, Blount disease)	30	44.8
Gastrointestinal tract pathology (chronic gastroduodenitis, sphincter of Oddi dysfunction, chronic cholecystitis, chronic pancreatitis, celiac disease)	16	23.9
Eye pathology (myopia, hyperopia, astigmatism, exocoria, dry eye syndrome)	14	20.9
Allergopathology (atopic dermatitis, urticaria, bronchial asthma)	11	16.4
Hernias of the abdominal wall (inguinal, umbilical)	10	14.9
Endocrine pathology (obesity grades 1-3, delayed sexual development, thyroid pathology)	8	11.9
Pathology of the heart and blood vessels (dilation of the aortic root, minor cardiac anomalies)	8	11.9
Pathology of the genital organs (hydrocele, varicocele, phimosis, synechiae of the penis)	8	11.9
Spina bifida	7	10.4
Chronic tonsillitis	7	10.4

Tuberculosis infection	4	6.0
Neurocirculatory dystonia	3	4.5
Epilepsy	1	1.5

As can be seen from Table 16 the most common concomitant pathologies are: pathology of the urinary system in 71.6%, pathology of the skeletal system in 44.8%, pathology of the gastrointestinal tract in 23.9%, pathology of the eyes in 20.9%.

§4.2 Features of manifestations of ADPKD in children at the first detection of cysts in the kidneys by ultrasound and **at the time of follow-up**

To assess the characteristics of the course of autosomal dominant polycystic kidney disease in children and adolescents, a follow-up study of 67 patients from 60 families was conducted.

The average age of children with ADPKD at the time of follow-up was 13.2±0.54 years, maximum 18 years, minimum 1.5 years (Table17).

Table 17

Distribution of 67 children and adolescents with ADPKD by age and gender at the time of follow-up

age (years)	number of children	%	boys	%	Girls	%
0-1	0	0	0	0	0	0
1,1-3	2	3.0	2	3.0	0	0
3.1-7	7	10.5	3	4.5	4	6.0
7.1- 15	24	35.8	16	23.8	8	12.0
15.1- 18	34	50.7	15	22.3	19	28.4
Total	67	100	36	53.6	31	46.4

The time from the moment of the first detection of cysts in the kidneys to the moment of follow-up (Table 4.5) in 67 patients ranged from 1 year to 18 years (on average 5.1±0.6 years).

Table 18

Time from the moment of first detection of kidney cysts to the moment of follow-up in 67 children and adolescents with ADPKD

years	number of children	%	boys	%	girls	%
1-5	46	68,67	25	37.33	21	31,34
5.1-10	7	10.45	4	5.97	3	4.47
10.1-15	11	16.41	7	10.45	4	5.97
15.1-18	3	4.47	0	0	3	4.47
total	67	100	36	53.75	31	46.25

In 25 (37.3%) of 67 children with ADPKD, there were no clinical (pain syndrome, arterial hypertension) and laboratory (changes in urine tests) signs of the disease at the first detection of cysts. Of the 25, in 4 children the reason for performing ultrasound that revealed cysts in the kidneys was antenatal suspicion of polycystic kidney disease, in 8 - pathology of other organs, in 13 - aggravated heredity for ADPKD. At the time of follow-up, clinical and laboratory signs of the disease were absent in 18 (26.9%) children.

Of the 67 children with ADPKD, 13 (19.4%) complained of pain syndrome at the first detection of cysts, and 28 (41.8%) at the time of follow-up. The average age of onset of complaints of pain in the abdomen/lower back/side was 12.5±0.63 years.

Changes in urine tests at the first detection of cysts were found in 38 (56.7%) of 67 children: proteinuria in 40.3%, leukocyturia in 37.3%, erythrocyturia in *6%* of cases. At the time of follow-up, changes in urine tests were found in 44 (65.7%) of 67 children: proteinuria in 46.3%, leukocyturia in 40.3%), erythrocyturia in 10.4% of cases.

Of the 67 children and adolescents at the time of follow-up, arterial hypertension was diagnosed in 14 (21%) (10 boys and 4 girls), of which 3 boys *(4.5%)* had hypertension when cysts were first detected (Table 19).

Table 19

Distribution of 14 probands with ADPKD by age and gender at the time of detection of arterial hypertension

Age (years)	General quantity children	%	Number of boys	%	Number of girls	%
0-1	0	0	0	0	0	0
1,1-3	0	0	0	0	0	0
3.1-7	0	0	0	0	0	0
7.1-10	0	0	0	0	0	0
10.1-15	10	71.4	8	57.1	2	14.3
15.1- 18	4	28.6	2	14.3	2	14.3
Total	14	100	10	71.4	4	28.6

Table 19 shows that in 71.4% of children with ADPKD, arterial hypertension syndrome was detected at the age of 10.1 to 15 years. The average age of children at the time of detection of hypertension was 13.98±0.41 years, the minimum age was 11 years, the maximum was 17 years. Stable arterial hypertension was detected in 5, labile - in 9 of 14 children and adolescents.

Arterial hypertension syndrome was detected in 14 children and adolescents: before the detection of cysts in 2 (one of them with glomerulonephritis), simultaneously with the detection of cysts in 1, within 15 years after the detection of cysts in 11 (of which: in one - within the first 5 years, in 3 - within 5 to 10 years, in 7 - within 10 to 15 years), (Table 20).

Table 20

Features of diagnostics of arterial hypertension syndrome and kidney cysts based on ultrasound results in 14 probands

	to detection of	simultaneously with detection	after detection of cysts		
			for the first	for	for

	cysts	cysts	time 5 years	5-10 years	10-15 years
quantity children	2	1	1	3	7
%	14.3	7.1	7.1	21.5	50.0

Of the 67 children, extrarenal manifestations of ADPKD were established at the first detection of cysts in 9 (13.5%) children, and at the time of follow-up in 21 (31.3%), of which 17 (25.3%) had one extrarenal manifestation, and 4 (6%) had combined lesions. Extrarenal manifestations are presented in the form of extrarenal cysts (liver and ovarian cysts), cardiac and vascular pathologies (minor cardiac anomalies, aortic root dilation), abdominal wall hernias (umbilical, inguinal).

The frequency of extrarenal manifestations in children with ADPKD at the first detection of cysts in the kidneys and at the time of follow-up is presented in Figure *.

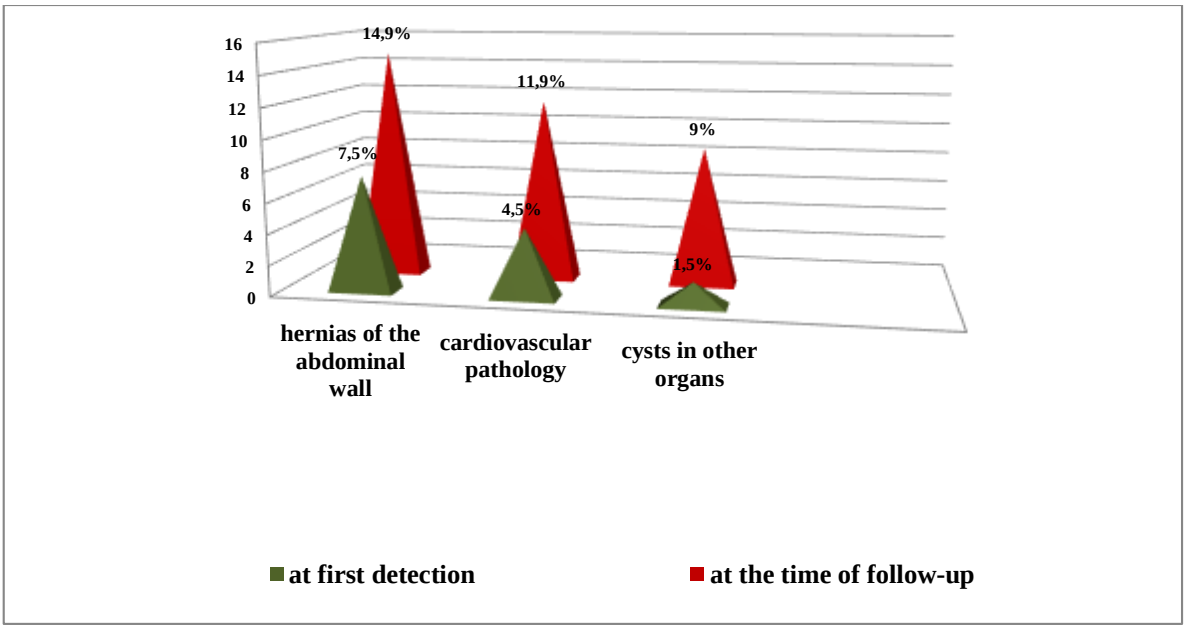


Figure 51* Frequency of extrarenal manifestations in 67 children with ADPKD at the first detection of cysts and at the time of follow-up.

It should be noted that liver cysts in children were detected only by CT or MRI; no liver cysts were detected by ultrasound. Of the 20 children , liver cysts

were detected in 4 (20%) by CT or MRI, and in 0% by ultrasound .

At the first detection of cysts in the kidneys, unilateral location of cysts was established in 27 (40.3%) children with ADPKD, bilateral - in 40 (59.7%), at the time of follow-up, unilateral location was established in 3 (4.5%) children, bilateral - in 64 (95.5%), (Figure 52*).

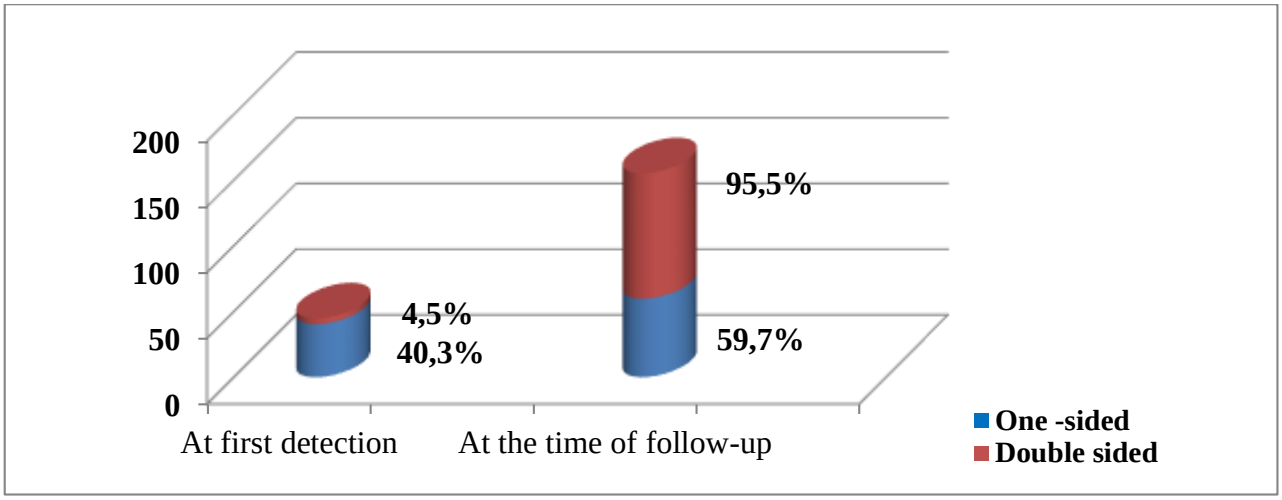


Figure 52* Features of the location of cysts in the kidneys according to ultrasound at the first detection of cysts and at the time of follow-up of 67 probands.

Over the years, the percentage of children with bilateral cysts according to ultrasound increases, and after 5 years from the moment of the first detection of cysts it reaches 100% (Figure 53).

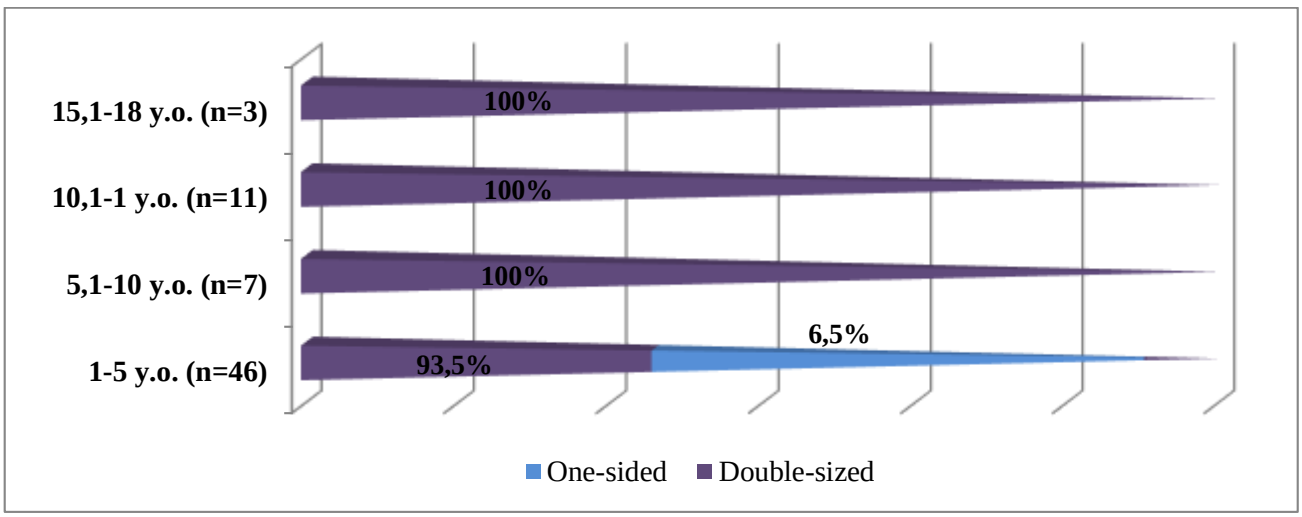


Figure 53* Frequency (in %) of unilateral and bilateral location of cysts at the time of follow-up of 67 children.

Multiple kidney cysts were diagnosed in 10 (14.9%) of the 67 children with

ADPKD at first detection, and single cysts were found in 57 (85.1%) of the 67 children with ADPKD. At the time of follow-up, multiple kidney cysts were detected in 28 (41.8%), and single cysts were found in 39 (58.2%) of the 67 children with ADPKD (Figure 53).

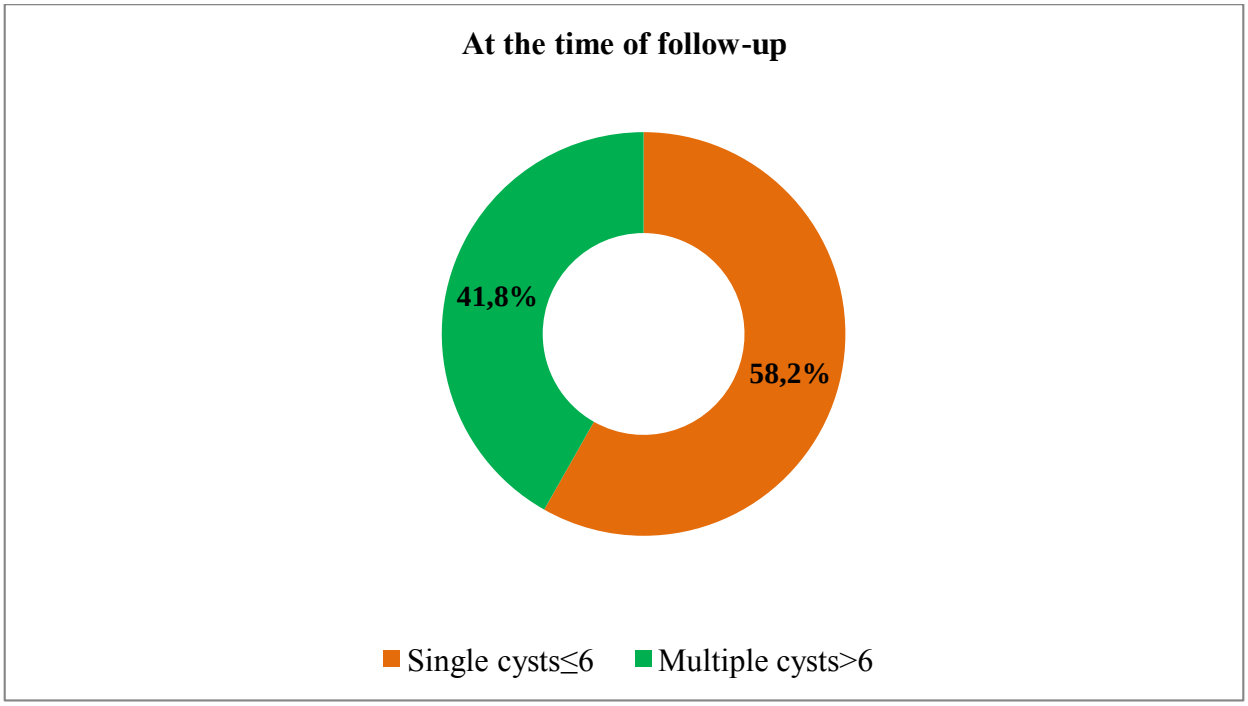


Figure 54* **Dynamics of the number of cysts according to ultrasound in 67 children with ADPKD**

Over the years, the percentage of children with multiple cysts increases and, if the time since the first detection of cysts is more than 15 years, reaches 100% (Figure 54*).

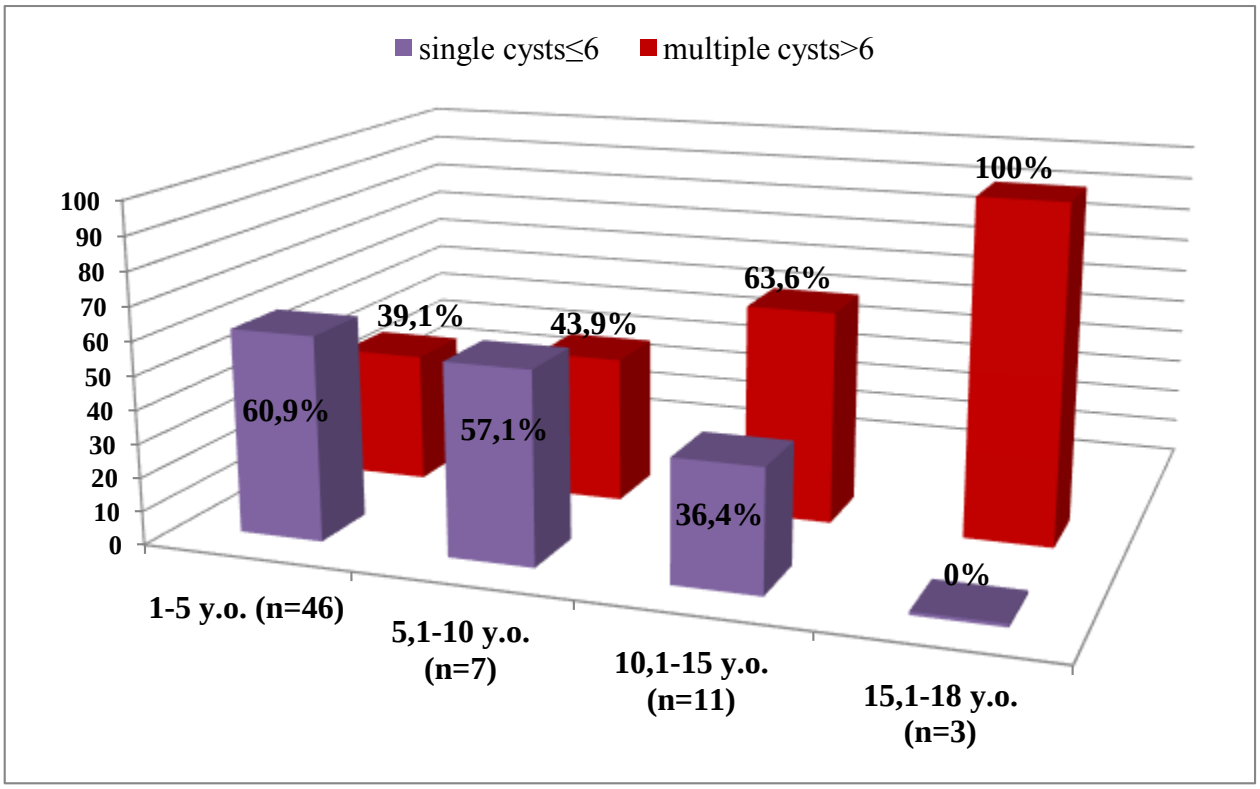


Figure 54*. Frequency of single and multiple cysts in the kidneys at the time of follow-up of 67 children with ADPKD

At the first detection of cysts in the kidneys of 43 children with ADPKD, the maximum diameter of the cysts was 1.89 ± 0.19 cm (from 0.2 cm to 5.07 cm), at the time of follow-up in 64 children - 2.76 ± 0.14 cm (from 0.3 cm to 6.8 cm), the differences are significant ($p < 0.001$).

The average kidney length (the average length of the left and right kidneys according to ultrasound) in 36 children with ADPKD at the first detection of cysts was 9.24 ± 0.3 cm, in 62 children at the time of follow-up - 10.8 ± 0.2 cm, the differences are significant ($p < 0.001$).

The data on the first detection of cysts and at the time of follow-up in 67 children is presented in summary table 21.

Table 21

Comparative characteristics of ADPKD at the first detection of cysts and at the time of follow-up of 67 probands

	at first detection of cysts		at the time of follow-up		level significance
sign	Quantity children	%	Quantity children	%	R
absence of clinical and laboratory signs of ADPKD	25	37.3	18	26.9	p>0.05
Presence of clinical and/or laboratory signs of ADPKD	42	62.7	49	73.1	p>0.05
presence of pain syndrome (stomach/lower back/side)	13	19.4	28	41.8	p<0.001
presence of changes in urine tests	38	56.7	44	65.7	p>0.05
presence of proteinuria	27	40.3	31	46.3	p>0.05
presence of leukocyturia	25	37.3	27	40.3	p>0.05
presence of erythrocyturia	4	6.0	7	10.4	p>0.05
AHsyndrome	3	4.5	14	21.0	p<0.01
extrarenal manifestations	9	13.5	21	31.3	p<0.05
One-sided location of cysts	27	40.3	3	4.5	p<0.01
bilateral location of cysts	40	59.7	64	95.5	p<0.01

multiple cysts	10	14.9	28	41.8	p<0.01
single cysts	57	85.1	39	58.2	p<0.01

A strong direct correlation was found in 36 children with ADPKD between the increase in the maximum diameter of cysts in the kidneys (from detection to the time of follow-up) and the time since the first detection of cysts.

Figure 4.7 Correlation between the increase in the maximum diameter of kidney cysts and the time since the first detection of cysts (r=0.76; p<0.001).

Regression analysis revealed an annual increase in the maximum diameter of kidney cysts according to ultrasound by 0.21 ± 0.03 cm in children with ADPKD.

A strong direct correlation was established in 40 children with ADPKD between the increase in the average length of the kidneys (from the moment of detection of cysts to the moment of follow-up) and the time since the first detection of cysts in the kidneys.

Time since first detection of kidney cysts (years) Figure 4.8 Correlation between the increase in average kidney length and the time since first detection of kidney cysts (r=0.85; p<0.001).

Regression analysis showed an annual increase in the average length of the kidneys according to ultrasound by 0.42 ± 0.05 cm in children with ADPKD.

A comparative analysis of the volume of the left and right kidneys was conducted in 20 children with ADPKD and 75 healthy children according to data from Al-Khatib SS (2006) (Table 22).

Table 22

Kidney volume in 20 probands with ADPKD and 75 healthy children

	Volume (cm^3) of the left kidney in patients with ADPKD	Volume (cm^3) of the left kidney in healthy people children	level significant you (R)	Volume (cm^3) right kidneys in patients with ADHS	Volume (cm^3) right kidneys at healthy children	level significant you (R)
3-6 years	61.0 ±10.2 (n=3)	45.5±3.1 (n=24)	p>0.05	71.3±15.7 (n=3)	43.0±2.6 (n=24)	p>0.05
7-11 years	109.1±23.9 (n=3)	66.2±3.7 (n=26)	p<0.05	64.9±5.4 (n=3)	70.2±6.6 (n=26)	p>0.05
12-17 years	231.9±55.2 (n=14)	106.1±5.1 (n=25)	p<0.05	160.7±25.0 (n=14)	98.9±6.0 (n=25)	p<0.05

As can be seen from Table 4.9, in all age groups, the volume of the kidneys is greater in children with ADHS, the volume of the left kidney in children aged 7-11 years and the volume of both kidneys in children aged 12-17 years are statistically significantly greater than in healthy children.

A strong direct correlation was found between the maximum cyst diameter and kidney volume in 20 probands with ADHS.

There is a moderate direct correlation between the average volume of the kidneys at the time of follow-up and the time since the first detection of cysts in the kidneys (Figure 4.10).

Figure 4.10 Correlation between the average kidney volume at the time of follow-up and the time (in years) since the first detection of kidney cysts in 20 probands with ADPKD (r=0.66; p<0.001).

§4.3. Features of the course of ADPKD in children with and without arterial hypertension

Of the 67 children and adolescents, arterial hypertension was detected in 14

(21%), including 10 boys and 4 girls, a ratio of 2.5:1. The average age of children at the time of detection of hypertension was 13.98±0.41 years, the minimum age was 11 years, the maximum was 17 years.

The average age at the time of detection of kidney cysts in children with arterial hypertension was 6.7±1.58 years, in children without arterial hypertension - 8.7±0.7 years. At the time of follow-up, in 14 children with arterial hypertension, according to the ultrasound results, bilateral location of cysts was established in 100% of cases: multiple - in 8 (57.1%), single - in 6 (42.9%). At the time of follow-up, out of 53 children without arterial hypertension, bilateral location of cysts was established in 50 (94.3%). Multiple cysts were detected in 20 (37.7%), single - in 33 (62.3%). Pain syndrome was detected in 6 (42.9%), changes in urine tests in 10 (71.4%) of 14 children with hypertension.

The maximum diameter of kidney cysts in children with arterial hypertension is significantly greater (3.69±0.42 cm) than in children without arterial hypertension (2.4±0.16 cm), ($p<0.01$). Significant differences in the average length of the kidneys were found among children and adolescents with (11.94±0.64 cm) and without hypertension (10.45±0.22 cm), ($p<0.05$).

In two adolescents with polycystic kidney disease and hypertension, a moderate (55 ml/min/1.73m2) and significant (32 ml/min/1.73m2) decrease in SCF according to the Schwartz formula (SHA and SB stages of CKD) was found, including one patient with glomerulonephritis. There were no significant differences in SCF among children with and without arterial hypertension, calculated using the Schwartz formula (115.3±11.3 ml/min/1.73m2 and 116.3±4.5 ml/min/1.73m2, respectively) or in endogenous creatinine clearance (91.8±10.1 ml/min/1.73m2 and 112.5±8.5 ml/min/1.73m2, respectively) ($p>0.05$). A comparative assessment of the manifestations of ADPKD in children with and without hypertension is presented in summary table 23.

Table 23

Manifestations of ADPKD in 14 children with and 53 without arterial hypertension

	children with hypertension (n=14)		children without hypertension (n=53)		Level significance
sign	quantity children	%	Quantity children	%	R
pain syndrome (abdomen/lower back/side)	6	42.9	22	41.5	t=0.09; p>0.05
changes in urine tests	10	71.4	34	64.2	t=0.5; p>0.05
unilateral cysts	0	0	3	5.7	t=l,8;p>0,05
bilateral cysts	14	100	50	94.3	t=l,8;p>0,05
multiple cysts	8	57.1	20	37.7	t=l.3; p>0.05
single cysts	6	42.9	33	62.3	t=l,3;p>0,05
maximum diameter of kidney cysts (cm)	3.69±0.42		2.4±0.16		t=2.87; p<0.01
average kidney length (cm)	11.94 ±0.64		10.45±0.22		t=2.2; p<0.05
average age of cyst detection (years)	b.7±1.58		8.7 ±0.7		t=l,2;p>0,05
SCF by endogenous creatinine clearance (ml/min/1.73m")	91.8 ± 10.1		112.5 ±8.5		t=1.6; p>0.05
SCF according to the Schwartz formula	115.3±11.3		116.3±4.5		t=0.08; p>0.05

(ml/min/1.73m")			

Thus, among children with ADPKD, with and without arterial hypertension, reliable differences were found in the maximum diameter of cysts in the kidneys and in the average length of the kidneys.

§4.4. Features of the course of ADPKD in **children and adolescents depending on the age at the time of detection of cysts**

Very early detection of cysts (before 18 months of age) was found in 13 (4 girls and 9 boys) of 67 children and adolescents with ADPKD. The reason for the first ultrasound examination of the kidneys in most cases was an aggravated family history and antenatal suspicion of polycystic kidney disease. The average birth weight was 3075±139.7 g, the average body length was 51±0.58 cm. The follow-up of 13 children with very early detection of cysts averaged 9.3±1.8 years, and 54 children with later detection (after 18 months) - 4.1±0.5 years.

In 13 (100%) children with very early detection, bilateral renal cysts were diagnosed, of which 9 (69.2%) had multiple cysts and 4 (30.8%) had single cysts. Of the 54 children with later detection (after 18 months), bilateral cysts were found in 51 (94.4%). Multiple renal cysts were found in 19 (35.2%), and single cysts were found in 35 (64.8%). Pain syndrome was found in 5 (30.8%), and changes in urine tests were found in 5 (30.8%) of the 13 children with very early detection of cysts.

significant differences between the maximum diameter of kidney cysts in children with very early detection (3.08±0.53 cm) and with later detection (2.67±0.19 cm) ($p>0.05$). The average kidney length in children with very early detection of cysts (11.03±0.79 cm) did not differ significantly from the average kidney length (10.7±0.22 cm) in children with later detection ($p>0.05$).

The frequency of hypertension in children with very early detection of cysts (30.8%) does not differ significantly from the frequency of hypertension in children with later detection (18.5%) ($p>0.05$).

At the time of follow-up (18 and 5 years), a slight decrease in SCF (77 and 84 ml/min/1.73 m2) according to the Schwartz calculation formula (stage II CKD)

was found in 2 children with very early detection of cysts. There were no significant differences in SCF among children with very early and later detection of cysts, calculated using the Schwartz formula (129.5±16.2 ml/min/1.73 m^2 and 118.9±3.4 ml/min/1.73 m^2 , respectively) and in endogenous creatinine clearance (114.8±19.26 ml/min/1.73 m2 and 108±6.3 ml/min/1.73 m^2 , respectively) (p>0.05).

A comparative assessment of the manifestations of ADPKD in children with very early detection and with later detection (after 18 months) of kidney cysts is presented in summary table 24.

Table 24

Manifestations of ADPKD in children with very early detection of cysts and with later detection of cysts in the kidneys

	children with very early identification cysts (n=13)		children with more late identification cysts **(n=54)**		level significance
sign	number of children	%	number of children	%	R
AHsyndrome	4	30.8	10	18.5	t=0.86; >0.05
pain syndrome (abdomen/lower back/side)	5	38.5	23	42.6	**1=0.3;** p>0.05
changes in urine tests	6	46.2	38	70.4	t=l,5;p>0,05
unilateral cysts	0	0	3	5.6	t=l,8;p>0,05
bilateral cysts	13	100	51	94.4	t=l.8; p>0.05
multiple cysts	9	69.2	19	35.2	t=2.3; p<0.05
single cysts	4	30.8	35	64.8	t=2.3; p<0.05
maximum diameter of	3.08±0.53		2.67±0.19		t=0.73;p>0.05

kidney cysts (cm)			
average kidney length (cm)	11.03±0.79	10.7±0.22	t=0.4; p>0.05
SCF by endogenous creatinine clearance (ml/min/1.73 m'')	114.8±19.2b	108±6.3	t=0.3; p>0.05
SCF according to the Schwartz formula (ml/min/1.73m')	129.5±16.2	118.9±3.4	t=0.6; p>0.05

Thus, children with earlier detection of cysts are significantly more likely to have multiple cysts in the kidneys than children with later detection of cysts.

CHAPTER V. FUNCTIONAL STATE OF THE KIDNEYS AND STAGES OF CHRONIC KIDNEY DISEASE IN CHILDREN WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

§5.1. Results of assessment of the functional state of the kidneys in children and adolescents with autosomal dominant polycystic kidney disease

The functional state of the kidneys was assessed in 67 children and adolescents with autosomal dominant polycystic kidney disease. The SCF was studied by endogenous creatinine clearance (Reberg-Tareev test) and the Schwartz calculation formula, concentration and excretion functions by the Zimnitsky test, and kidney function by regulating acid-base balance.

Of the 67 children, 20 (29.9%) had glomerular hyperfiltration (SCF> 140 ml/min/1.73 m2) at the first detection of cysts. A decrease in the glomerular filtration rate was found in 1 child with ADPKD and mesangioproliferative glomerulonephritis (SCF by endogenous creatinine clearance 76 ml/min/1.73 m2, according to the Schwartz calculation formula 82 ml/min/1.73 m2). In 46 children with ADPKD, at the first detection of cysts, the SCF by endogenous creatinine clearance averaged 103.8±7.1 ml/min/1.73 ^{m2} , according to the Schwartz calculation formula 113±2.4 ml/min/1.73 m2.

In comparison with normal values of SCF by endogenous creatinine clearance (118±18 ml/min/1.73m2) and by the Schwartz calculation formula (133±27 ml/min/1.73m2), no significant differences in SCF were found (p>0.05).

At the time of follow-up, 12 out of 67 children with ADPKD (17.9%) had glomerular hyperfiltration (SCF> 140 ml/min/1.73m2). The glomerular filtration rate was reduced in 4 children (SCF by endogenous creatinine clearance 30.50.61.72 ml/min/1.73m2, according to the Schwartz calculation formula 32.55.77.84 ml/min/1.73m2). In 51 children with ADPKD, at the time of follow-up, the SCF by endogenous creatinine clearance averaged 100.7±4.2 ml/min/1.73m2, according to the Schwartz calculation formula 112.6±1.8 ml/min/ $^{1.73m2}$.

In comparison with normal values of SCF by endogenous creatinine clearance (118±18 ml/min/1.73m2) and by the Schwartz calculation formula (133±27 ml/min/1.73m2), no significant differences in SCF were found (p>0.05).

Table 25

Evaluation of SCF in 46 children with ADPKD when cysts were detected and 51 children with ADPKD at the time of follow-up compared with normal values

1 GFR (ml/min/ 1.73 m)	In children with ADPKD	Norm	Significance level (P)
By endogenous creatinine clearance (Rehberg-Tareev test) when detecting cysts (n=46)	103.8±7.1	118±18	p>0.05
By endogenous creatinine clearance (Rehberg-Tareev test) at the time of follow-up (n=51)	100.7±4.2		p>0.05
According to the calculation formula Schwartz when detected Cysts (n=46)	113±2.4	133±27	p>0.05
According to the calculation formula Schwartz at the moment Follow-up (n=51)	112.6±1.8		p>0.05

When comparing the SCF indices in children with ADPKD at the first detection of cysts and at the time of follow-up, no reliable differences were found (Table 26).

Table 26

Comparative assessment of SCF in children with ADPKD using endogenous creatinine clearance and the Schwartz calculation formula.

2 GFR (ml/min/ 1.73 m)	At first detection of cysts (p=4b)	At the moment catamnesis (n=51)	Level significance (R)
By endogenous creatinine clearance (Rehberg-Tareev test)	103.8±7.1	100.7±4.2	p>0.05
According to the calculation formula Schwartz	113±2.4	112.6±1.8	p>0.05

We compared the Reberg-Tareev test results in 46 children.
with ADPKD at the first detection of cysts and in 51 children with ADPKD at the time of follow-up according to Student's t- test, the results of which are presented in Table 27.

Table 27

Reberg-Tareev test indices in children with ADPKD at the first detection of cysts and at the time of follow-up

Indicators	At first detection of cysts (n=46) M±t	At the time of follow-up (n=51) M±t	Level significance (R)
daily diuresis (ml)	1227.5±108.7	1311.1±98.9	1=0.56 p>0.05
minute diuresis (ml/min)	0.86±0.1	0.89±0.05	1=0.27 p>0.05
plasma creatinine (mmol/l)	0.07±0.003	0.073±0.003	1=0.71 p>0.05
urine creatinine (mmol/l)	7,61±0,8	8.38±0.59	t=0.77 p>0.05
tubular reabsorption (%)	99.1 ±0.17	98.9±0.18	t=0.81 p>0.05

SCF (ml/min/ $^{1.73m2}$)	120.8±8.7	106.7±6.8	1=1.27 p>0.05

The levels of daily diuresis, minute diuresis, blood creatinine, urine creatinine, tubular water reabsorption at the first detection of cysts and at the time of follow-up were within normal values; no statistically significant differences were found.

The concentration and excretion functions of the kidneys in children with ADPKD were assessed using the Zimnitsky test. Impairments in the concentration and excretion functions of the kidneys (in the form of hyposthenuria, nocturia, and polyuria) in children with ADPKD were found both at the first detection of cysts in the kidneys and at the time of follow-up. At the first detection of cysts, impairments according to the Zimnitsky test were found in 10.4%, at the time of follow-up in 23.9% ($p<0.05$), (Figure55 *).

Thus, at the first detection of cysts, 7 out of 67 children (10.4%) were found to have disorders of concentration and excretory functions in the form of hyposthenuria (relative density 1011±3.2), nocturia (daytime diuresis < nighttime diuresis), at the time of follow-up, 16 out of 67 children (23.9%) had disorders of concentration and excretion functions in the form of hyposthenuria (relative density 1009±1.2), nocturia (daytime diuresis < nighttime diuresis), polyuria (>1500 ml/m2 / day).

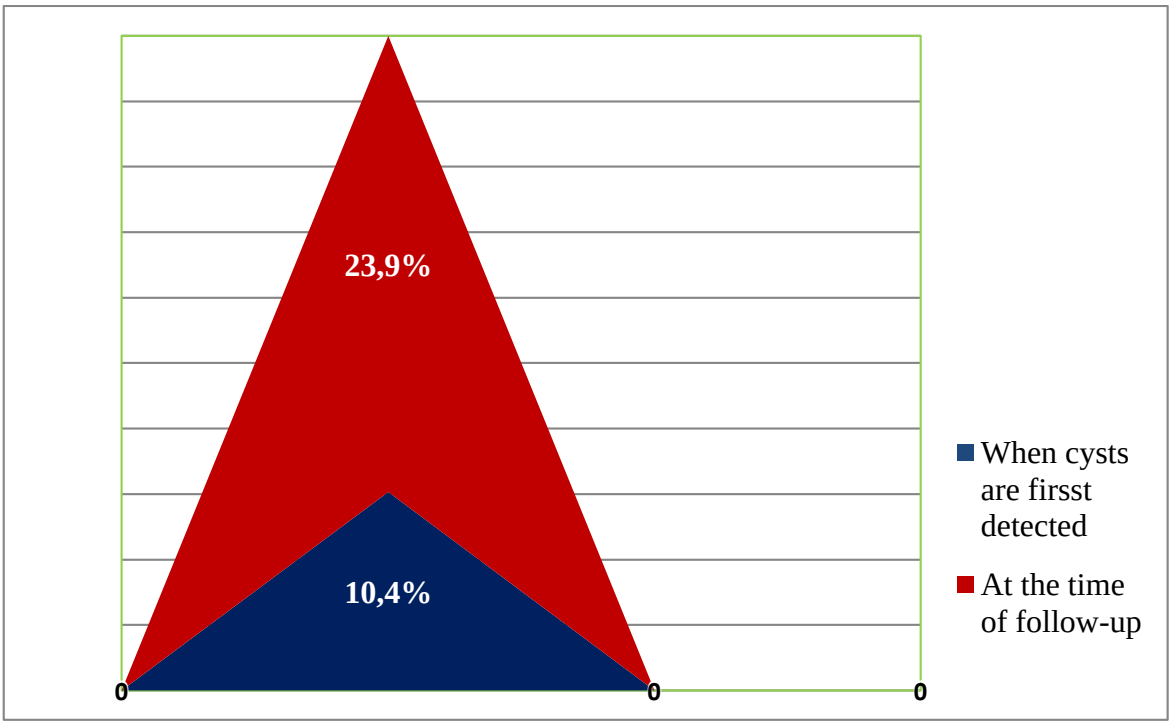


Figure 55* Frequency (in %) of disturbances of concentration and excretory functions of the kidneys according to Zimnitsky's test at the first detection of cysts and at the time of follow-up of 67 children with ADPKD

Renal tubular metabolic acidosis in children with ADPKD was detected in 14.9% of cases at the first detection of cysts and in 19.4% of cases at the time of follow-up.

Tables 28 and 29 present a comparative assessment of the acid-base balance indicators in children with ADPKD with acid-base imbalances and normal values at the first detection of cysts and at the time of follow-up.

Table 28

Acid-base balance indicators in children with ADPKD who have acid-base balance disorders at the first detection of cysts

KOS indicator	at first detection of cysts (n=10)	normal indicator	Level significance (p)
Rn	7.35±0.03	7.35-7.45	p>0.05
pCO2 (mmHg)	38.6±4.9	35-45	p>0.05
BEecf (mmol/l)	-4.65±0.8	±2.3	p<0.05
HCO3 (mmol/l)	20.3±1.1	22-24	p<0.05
horn (mmHg)	77.4±5.4	70-115	p>0.05

Table 29

Acid-base balance indicators in children with ADPKD who have acid-base balance disorders at the time of follow-up

KOS indicator	at the time of follow-up (n=13)	normal indicator	level of significance (p)
rn	7.33±0.04	7.35-7.45	p>0.05
pCO2 (mmHg)	37.05±3.5	35-45	p>0.05
BEecf (mmol/l)	-5.9±2.4	±2.3	**p<0.05**
HCO 3 (mmol/l)	19.5*2.2	22-24	**p<0.05**
horn (mmHg)	76.8±12.4	70-115	p>0.05

Renal tubular dysfunction is attributed to tubulointerstitial disorders resulting from the development and growth of cysts in the kidneys in children with ADPKD.

§5.2. Stages of chronic kidney disease in children with autosomal dominant polycystic kidney disease

In children with ADPKD, the stages of chronic kidney disease were determined based on the level of SCF using the Schwartz calculation formula , at the first detection of cysts in the kidneys and at the time of follow-up (Table 30).

Table 30.

Distribution of 67 children by stages of chronic kidney disease at the first detection of cysts and at the time of follow-up

	At first detection of cysts (n=67)		At the time of follow-up (n=67)	
CKD stage 2 (SCF in ml/min/1.73 m)	number of children	%	quantity children	%
I (SCF> 90)	66	98.5	63	94

II (SKF 60-89)		1	1.5	2	3.0
III	A (SKF 45-59)	0	0	1	1.5
	B (SKF 30-44)	0	0	1	1.5
IV (SKF 15-29)		0	0	0	0
V (SCF < 15)		0	0	0	0

In 67 children with ADPKD, a predominance of stage I CKD was established both at the first detection of cysts (98.5%) and at the time of follow-up (94%).

At the first detection of cysts, stage II CKD (kidney damage with a slight decrease in SCF) was established in 1 16-year-old boy with ADPKD and mesangioproliferative glomerulonephritis.

At the time of follow-up, stage II CKD was diagnosed in 2 children (18 and 5 years old) with a very early onset of the disease. Stages SHA and SB CKD (kidney damage with a moderate and significant decrease in SCF) were diagnosed in 2 children (16 and 17 years old).

Taking into account the national recommendations “Chronic kidney disease: basic principles of screening, diagnosis, prevention and approaches to treatment” (2012), children with ADPKD were distributed in accordance with the ICD-10 coding (as amended in October 2007) [8].

Table 31

Correspondence of CKD stages to ICD-10 coding in children with ADPKD

		At first detection of cysts (n=67)		At the time of follow-up (n=67)	
Stage of CKD (ICD-10 code)		number of children	%	number of children	%
1 (N18.1)		66	98.5	63	94
II (N18.2)		1	1.5	2	3
III A	(N 18.3)	0	0	2	3
III B					

IV (N18.4)	0	0	0	0
V (N18.5)	0	0	0	0

Tables 31 and 32 present the state of kidney function by stages.

CKD in 67 children at the first detection of cysts and at the time of follow-up.

Table 32

Renal function status by CKD stages in 67 children with ADPKD at first detection of cysts

Stage of CKD	Signs of impaired kidney function
I (n=66)	SCF by the Schwartz calculation formula > 90 ml/min/1.73 m2, SCF by endogenous creatinine clearance 103.8±7.1 ml/min/1.73 m2, glomerular hyperfiltration in 30.3%, hyposthenuria in 9.1%, renal tubular metabolic acidosis in 13.6%
P(n=1)	SCF by the Schwartz calculation formula 60-89 ml/min/1.73 m2, SCF by endogenous creatinine clearance 76 ml/min/1.73 m2, blood creatinine 0.142 mmol/l, urea 10.4 mmol/l, uric acid 0.49 mmol/l, electrolyte disturbances, increased parathyroid hormone concentration in the blood, hyposthenuria, nocturia, polyuria, renal tubular metabolic acidosis

Table 33

The state of renal function by stages of CKD in 67 children with ADPKD at the time of follow-up

Stage CKD	Signs of impaired kidney function
I (n=63)	GFR according to the Schwartz calculation formula > 90 ml/min/1.73 m^2, SCF by endogenous creatinine clearance 100.7±4.2 ml/min/1.73 m2, glomerular hyperfiltration in 19%, hyposthenuria in 19%, renal tubular metabolic acidosis in 14.3%

II (n=2)	Schwartz calculation formula 60-89 ml/min/1.73 m2, SCF according to endogenous creatinine clearance 61 and 72 ml/min/1.73 m, hyposthenuria in 100%, renal tubular metabolic acidosis in 100%
III A(n=1)	SCF by the Schwartz calculation formula 45-59 ml/min/1.73 m, SCF by endogenous creatinine clearance 50 ml/min/1.73 m", blood creatinine 0.165 mmol/l, urea 11.3 mmol/l, uric acid 0.58 mmol/l, electrolyte disturbances, increased parathyroid hormone concentration in the blood, hyposthenuria, nocturia, polyuria, renal tubular metabolic acidosis
III B(n=1)	Schwartz calculation formula 30-44 ml/min/1.73 m", SCF by endogenous creatinine clearance 30 ml/min/1.73 m2, anemia, blood creatinine 0.4 mmol/l, urea 20.8 mmol/l, uric acid 0.43 mmol/l, electrolyte disturbances, increased parathyroid hormone concentration in the blood, hyposthenuria, polyuria, renal tubular metabolic acidosis

Below is a description of renal function in 2 children with ADPKD type III stage of CKD.

Boy I.N., age at the time of follow-up is 17 years. Kidney cysts were first described at the age of 16, in connection with an examination for mesangioproliferative glomerulonephritis (macrohematuria since the age of 4). During the last hospitalization, ultrasound showed bilateral cysts in the kidneys, with a maximum diameter of 2.7 cm. Arterial hypertension was detected since the age of 11. According to the results of nephrobiopsy: an increase in the volume of the mesangial matrix, moderate hypercellularity of a diffuse nature. Laboratory data revealed: hypoproteinemia (total protein 58 g/l), blood creatinine 0.165 mmol/l, urea 11.3 mmol/l, uric acid 0.58 mmol/l, hypercholesterolemia, hyperbetalipoproteinemia, electrolyte disturbances (hypocalcemia, hyperphosphatemia), elevated blood parathyroid hormone levels, metabolic acidosis (pH=7.38, pCO2 = 31.2 mmHg, HCO3=18.8 mmol/l, BEecf -6.5 mmol/l);

hyposthenuria (relative density 1002-1007), acidic urine reaction, polyuria, nocturia, hematuria; daily protein loss 3.88 g, SCF by endogenous creatinine clearance 50 ml/min/1.73 m~, by the Schwartz calculation formula 55 ml/min/1.73 m~. The clinical and laboratory symptom complex and the degree of renal dysfunction made it possible to establish the stage of CKD III A (renal damage with a moderate decrease in SCF) with the ICD-10 code N18.3.

Boy K.D., age at the time of follow-up is 16 years. Kidney cysts were first described at the age of 4, in connection with an examination for enuresis. During the last hospitalization, ultrasound showed bilateral kidney cysts, with a maximum diameter of 2 cm. Arterial hypertension was detected from the age of 14. According to laboratory data, the following was revealed: blood creatinine 0.4 mmol/l, urea 20.8 mmol/l, uric acid 0.43 mmol/l, hypercholesterolemia, hyperbetalipoproteinemia, electrolyte disturbances (hypocalcemia, hyperphosphatemia), elevated blood parathyroid hormone levels, hypochromic anemia (erythrocytes 3.41x10 "; hemoglobin 93 g/l; color index 0.81; serum iron 8.2 μmol/l); metabolic acidosis (pH=7.28, pCO2 = 41.2 mmHg, NCO3=18.7 mmol/l, BEecf -7.5 mmol/l); hyposthenuria (relative density 1003-1005), alkaline urine reaction, polyuria; daily protein loss 0.28 g., SCF by endogenous creatinine clearance 30 ml/min/1.73m~, by the Schwartz calculation formula 32 ml/min/1.73m". The clinical and laboratory symptom complex and the degree of renal dysfunction made it possible to establish stage III B CKD (renal damage with a significant decrease in SCF) with ICD-10 code N18.3 in a patient with ADPKD.

Thus, in children with ADPKD, disturbances of concentration and excretory functions and disturbances of acid-base balance regulation were revealed, both at the first detection of cysts and at the time of follow-up, which indicates tubulointerstitial changes. Disturbances of concentration and excretory functions of the kidneys according to Zimnitsky's test were established at the first detection in 10.4%, at the time of follow-up in 23.9% of cases, disturbances of acid-base balance regulation - in 14.9% and 19.4%, respectively. Glomerular hyperfiltration was established in 29.9% of cases at the first detection of cysts, in 17.9% of cases

at the time of follow-up.

When stratifying the severity of CKD by glomerular filtration rate, it was established in children with ADPKD that at the first detection of cysts in 1.5% and at the time of follow-up in 3%, kidney damage with a slight decrease in SCF (stage II) was found; in 3% at the time of follow-up, kidney damage with a moderate (stage III A) and significant (stage III B) decrease in SCF was found.

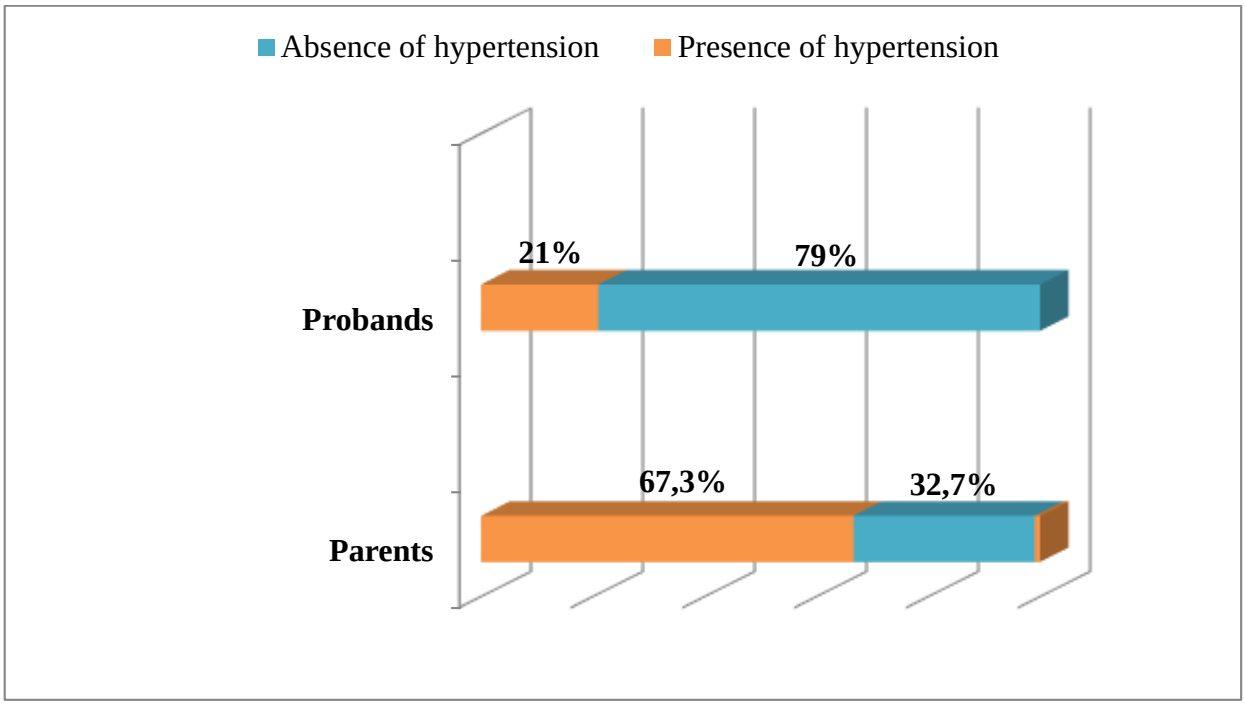
CHAPTER VI. COMPARATIVE ASSESSMENT OF THE FEATURES OF THE COURSE AND OUTCOME OF AUTOSOMAL-DOMINANT POLYCYSTIC KIDNEY DISEASE IN CHILDREN AND ADULTS, PATIENT SURVIVAL

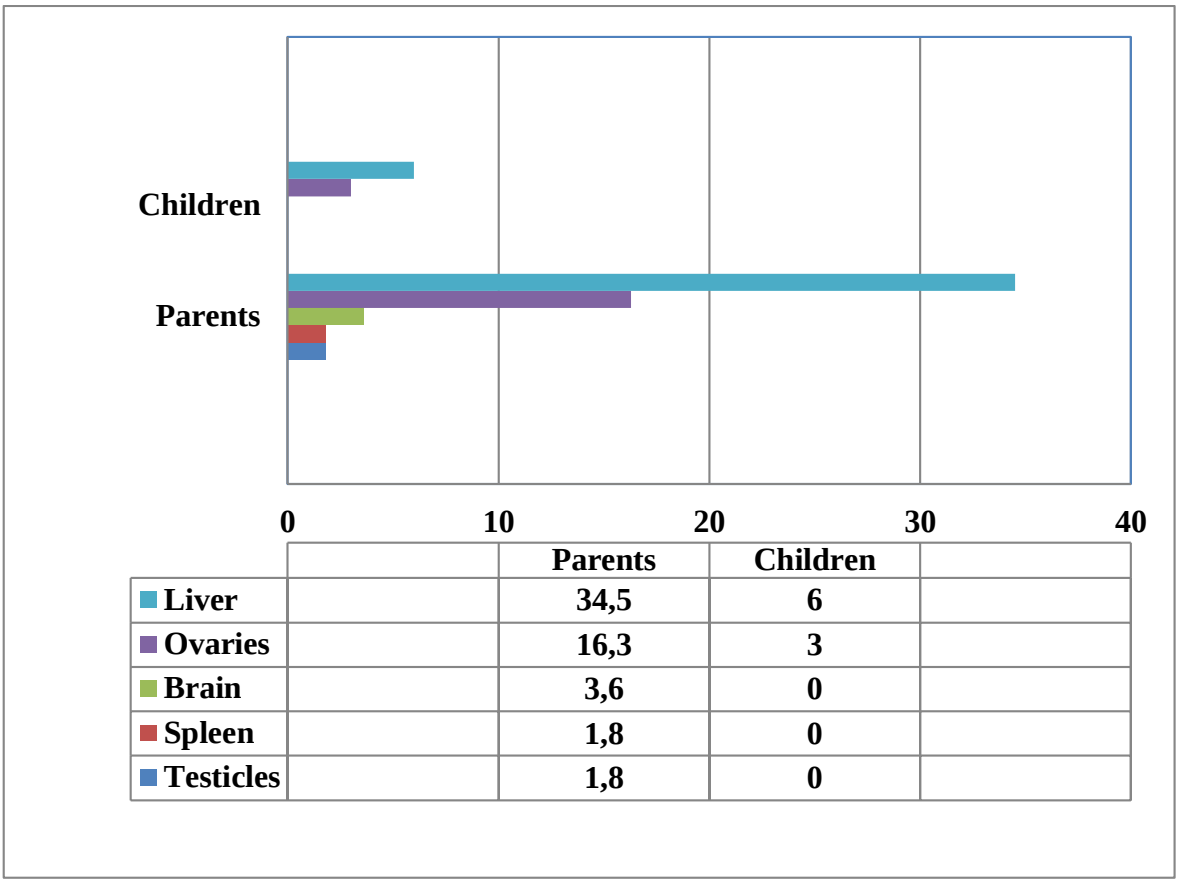
§ 6.1 Comparative assessment of the course and outcome of ADPKD in 67 children and 55 parents from 60 families

In 55 adults (parents) with ADPKD, the frequency of arterial hypertension syndrome, features of cystic lesions of other organs, disease outcome and structure of causes of death were analyzed.

Of the 55 adult patients, arterial hypertension was diagnosed in 37 (19 men and 18 women) and was stable. The development of arterial hypertension syndrome in adult patients (67.3%) was significantly more frequent than in children and adolescents (21%) in 60 families with ADPKD (Figure 6.1).

Figure IV.8 . Frequency of arterial hypertension (AH) syndrome in 67 probands and 55 parents with ADPKD.





	Parents	Children
Liver	34,5	6
Ovaries	16,3	3
Brain	3,6	0
Spleen	1,8	0
Testicles	1,8	0

In 67 children with ADPKD, no fatal outcomes, end-stage renal failure requiring renal replacement therapy, or cardiovascular complications were observed.

In contrast to children, 55 adults out of 60 families with ADPKD had fatal outcomes, development of cardiovascular complications and end-stage renal failure requiring renal replacement therapy.

Of the 55 adults, 8 (14.5%) died, including 5 from cardiovascular complications (myocardial infarction, cardiac tamponade, hemorrhagic stroke), and 3 from terminal renal failure. In 8 patients with ADPKD, cardiovascular complications were among the causes of death.

account for 62.5%, ESRD - 37.5%. Of the 55 adult patients with ADPKD, 8 (14.5%) receive renal replacement therapy due to the development of terminal renal failure (Figure 6.3).

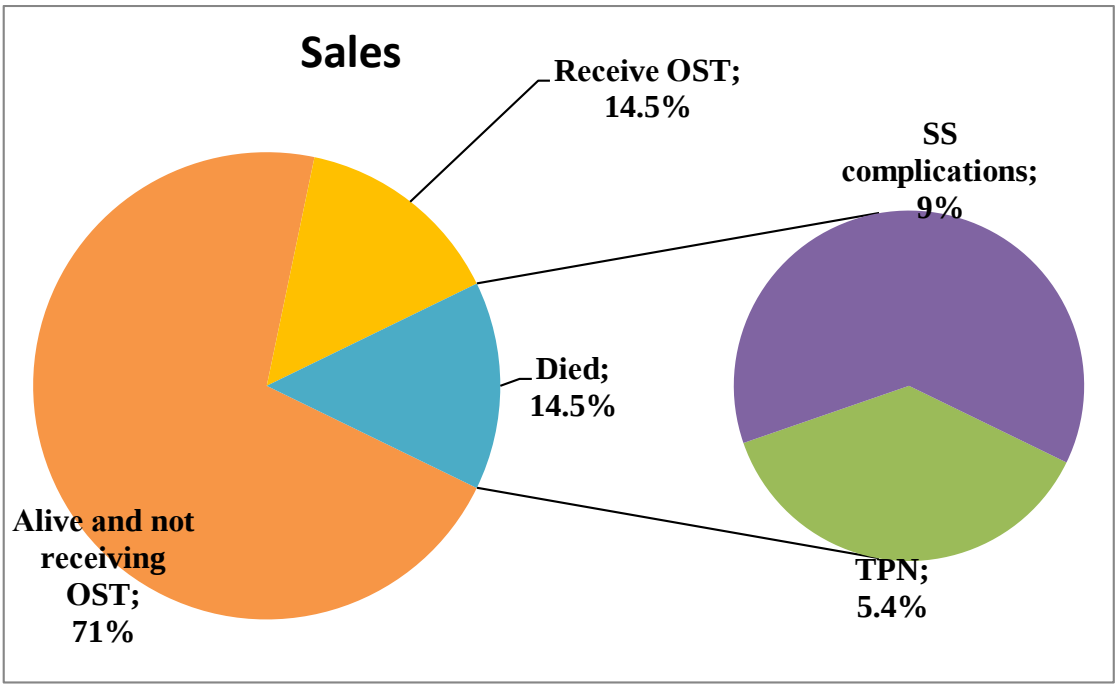


Figure 56* Outcome of ADPKD at the time of follow-up in 55 adult patients. (RRT - renal replacement therapy, ESRD - end-stage renal failure, CC - cardiovascular)

The main characteristics of the course and outcome of ADPKD in children and adults are presented in summary table 34.

Table 34

Summary table of the characteristics of the course and outcome of ADPKD in 67 children and 55 parents

	parents		children		level of significance
characteristics	quantity	%	quantity	%	R
AG	37	67.3	14	21.0	t=5.7; p<0.001
extrarenal cysts	29	52.7	6	9.0	t=6,l;p<0,001
need ZPT	8	14.5	0	0	t=3,l;p<0,01
Died	8	14.5	0	0	t=3,l;p<0,01

§ 6.2. Survival of patients with autosomal dominant polycystic kidney disease according to the moment method of E. Kaplan - P. Meier (1958)

The survival of 122 children and parents from 60 families with autosomal dominant polycystic kidney disease was calculated from the moment of the first detection of cysts using the non-interval method of E. Kaplan, P. Meier (1958). The non-interval method involves calculating survival rates at certain "points" in time, at each of which one outcome occurred (alive, died, dropped out of observation). The term "survivors" refers to patients with ADPKD who survived to the end of observation, having normal renal function or compensated renal failure that does not require hemodialysis. A life table was compiled to calculate the probability of survival (Table 6.2).

Note: the $t_{k\ values}$ in brackets contain the observation periods of surviving patients.

The result of the calculation is the probabilities 147 = 99%; 149 = 96%; 111 = 95%; 1113 =94%; 1114 = 93%; 1116 = 91%; 1420 = 87%; 1122 = 86%; 1124 = 84%; 1126 = 80%; 1129 =75%; 1131 = 66%; 1133 = 53% and 1135 = 0%.

The following notations are introduced in the table:

k - time interval number tr;

th - is the duration of the patient observation time interval (the beginning of all intervals coincides with the beginning of the time count), years;

N - is the number of observed patients at the end of the (k-1)-th interval;

nk - is the number of patients with a fatal outcome or development of ESRD in the time interval from th-1 to tz;

Wk - is the number of patients whose examination was not carried out in the time interval from - 1 to th, and in all subsequent observation intervals;

Nk -nk - the

number of observed patients at the end

interval tk; Wk)

$$p_k = \frac{N_k - n_k - w_k}{1 + N_k - n_k - w_k} -$$

Conditional probability of patient survival time interval from -1 to k.

11k - the probability (unconditional) of the patient's survival at time k.

Calculations of the probability of survival were carried out using the formula

$$l_{tk} = \prod_{i=1}^{k} \left(\frac{N_i - n_i - w_i}{1 + N_i - n_i - w_i} \right)$$

where as index i we take only the numbers corresponding to fatal outcomes or development of terminal renal failure requiring renal replacement therapy. In our table, for calculation 147 we took i = 7; for calculation 19 we took i = 7 and 9; for calculation 111 we took i = 7, 9 and - 11; for calculation 1113 we took i = 7, 9, 11 and 13; for calculation 1114 we took i = 7, 9, 11, 13 and 14; for calculation 1116 we took i 7, 9, 11, 13, 14 and 16; for calculation 120 we took i = 7, 9, 11, 13, 14, 16 and 20; To calculate 1422, i = 7, 9, 11, 13, 14, 16, 20, and 22 were taken; To calculate 1124, i = 7, 9, 11, 13, 14, 16, 20, 22, and 24 were taken; To calculate 1126, I = 7, 9, 11, 13, 14, 16, 20, 22, 24, and 26 were taken; To calculate 1129, i = 7, 9, 11, 13, 14, 16, 20, 22, 24, 26, and 29 were taken; To calculate 1131, we used i = 7, 9, 11, 13, 14, 16, 20, 22, 24, 26, 29, and 31; to calculate 1133, we used i = 7, 9, 11, 13, 14, 16, 20, 22, 24, 26, 29, 31, and 33; to calculate 1135, we used i = 7, 9, 11, 13, 14, 16, 20, 22, 24, 26, 29, 31, 33, and 35.

For the probability values we found 147, 149, 11, 413, 114, 1116, 120, 1122, 124,126, 1429, 1431 and 1433 according to the formula: m th = 1 ∑

$$[N, \quad -\eta, - w_1)(1 + N_1 - n - w_1)]^1 - 1 ! = 1$$

The corresponding values of the average errors were calculated: m171%;m92%;muu2%;m92%; m13=2%; m114=3%; M16=3%; m120=4%;

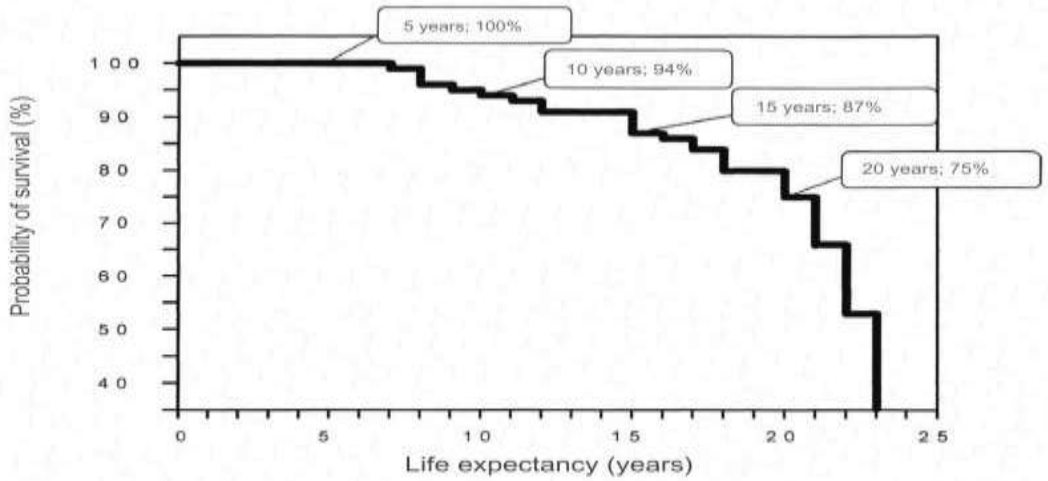
m122=4 %; m,24=5%; m126=6%; m.29=7%; t.31 = 11% and t133 = 15%.

Table 35

Life table (from first detection of cysts) of 122 patients with ADPKD

K	***tk,*** years	N_k	p_k	w_k	N_k-n_k--w_k	***Rk***	***hk,*** %
1	(1)	122	0	14	108	—	—
2	(2)	108	0	7	101	—	~
3	(3)	101	0	3	98	—	—
4	(4)	98	0	1	97	—	—
5	(5)	97	0	8	89	—	—
6	(6)	89	0	5	84	—	—
7	7	84	1	0	83	83/84	99
8	(7)	83	0	1	82	—	—
9	8	82	2	0	80	80/82	96
10	(8)	80	0	1	79	—	—
11	9	79	1	0	78	78/79	95
12	(9)	78	0	2	76	—	—
13	10	76	1	0	75	75/76	94
14	11	75	1	0	74	74/75	93
15	(P)	74	0	7	67	—	—
16	12	67	1	0	66	66/67	91
17	(12)	66	0	10	56	—	—
18	(13)	56	0	7	49	—	—
19	(14)	49	0	9	40	—	—
20	15	40	2	0	38	38/40	87
21	(15)	38	0	3	35	—	—
22	16	35	1	0	34	34/35	86
23	(16)	34	0	6	28	—	—
24	17	28	1	0	27	27/28	84
25	(17)	27	0	5	22	—	—

26	18	22	1	0	21	21/22	80
27	(18)	21	0	1	20	—	—
28	(19)	20	0	3	17	—	—
29	20	17	1	0	16	16/17	75
30	(20)	16	0	8	8	—	—
31	21	8	1	0	7	7/8	66
32	(21)	7	0	2	5	—	—
33	22	5	1	0	4	4/5	53
34	(22)	4	0	3	1	-	—
35	23	1	1	0	0	-	0



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6 Figure 6.4 Probability of survival of 122 children and parents from 60 families with ADPP from the moment of first detection of cysts.

The horizontal axis of the graph shows the time period (measured in years) from the start to the end of observation of the patient (if the patient is alive) or until his death (or the development of end-stage renal failure requiring renal replacement therapy). The vertical axis of the graph shows the survival probability (a value in the range from 100% to 0%).

The average period from the moment of detection of cysts to the end of observation in 122 patients with ADPKD was 11.14 ± 0.6 years.

Thus, the survival probability of 122 children and parents with autosomal dominant polycystic kidney disease was: 5-year - 100%, 10-year - 94%, 15-year - 87%, 20-year - 75%.

DISCUSSION

The work was carried out at the Department of Surgery, Urology, Anesthesiology and Resuscitation at the ASMI Clinic.

The aim of the work was to study the follow-up of children and adults (parents) in families with autosomal dominant polycystic kidney disease for early diagnosis of renal and extrarenal manifestations, course and outcome.

To form the study group, we initially assessed the ultrasound image of the urinary system organs of 189 members of 79 families, in which at least one child was admitted with a diagnosis of "polycystic kidney disease" by the referring institution. After verification, the diagnosis of "polycystic kidney disease" was confirmed in 133 members of 71 families: 78 children and adolescents (probands) aged 3 months to 18 years and 55 adults (parents) aged 30 to 55 years. In order to establish the type of inheritance of polycystic kidney disease, a genealogical analysis of 71 families was performed. In 55 families, a clear dominant inheritance was established (the presence of the disease in at least two generations: in relatives of both sexes of the 1st and/or 2nd degree of kinship). In 16 families, it was not possible to clearly establish the type of inheritance due to the absence of the disease in relatives of the 1st and/or 2nd degree of kinship. In 5 of 16 probands with an unspecified type of inheritance, due to the presence of bilateral multiple cysts (more than 6) in the kidneys, the presence of denovo mutation was assumed and they were included in the main study group. Of 67 children and adolescents, 5 (7.4%) had an uncomplicated family history. Literature data indicate that denovo mutations in ADPKD account for 4-10% [13,16,23,35].

The study included 122 members (67 children and adolescents and 55 adults) of 60 families with autosomal dominant polycystic kidney disease. Among the 67 children and adolescents (probands), 36 (53.7%) were boys and 31 (46.3%) were girls aged from 3 months to 18 years. Among the 55 adults (parents), 26 (47.3%) were men and 29 (52.7%) were women aged from 30 to 55 years. The ratio of male to female patients was 1.03:1.

According to the pedigrees, autosomal dominant polycystic kidney disease

was diagnosed in 10 siblings and 86 relatives of 2-4 degrees of kinship. Four probands gave birth to children (aged 1 to 4 years), two of whom (a boy and a girl) were diagnosed with ADPKD, and two (a boy and a girl) had no kidney cysts at the time of follow-up. Thus, in 60 families, 220 members are known to have been diagnosed with autosomal dominant polycystic kidney disease, including 118 women and 102 men (sex ratio -1.16:1).

Our data indicate a slight predominance of men in the study group and, conversely, a slight predominance of women in the total number of patients (according to pedigrees), which allows us to conclude that autosomal dominant polycystic kidney disease occurs with equal frequency in men and women. This is consistent with the literature data [23,47].

The disease was inherited from the father in 33 probands and from the mother in 29 probands. At the time of the first detection of kidney cysts, only 50 of the 62 probands with ADPKD had information about an aggravated family history. The parents of 12 probands (11 families) learned about the disease only after examination in connection with the detection of kidney cysts in children. The age at detection of cysts in 55 adults ranged from 17 to 53 years, on average 29.4±1.3 years. This confirms the fact that not all patients with ADPKD develop clinical manifestations of the disease simultaneously with the appearance of kidney cysts [33,51].

The work is based on the materials of the study of the features of clinical manifestations, course and outcome of autosomal dominant polycystic kidney disease in families in children and parents. A follow-up study of 67 children and adolescents (probands) with ADPKD was conducted to determine the age at the time of the first detection of cysts in the kidneys, the structure of extrarenal manifestations, features of clinical manifestations at the first detection of cysts and at the time of follow-up, features of the dynamics of cyst enlargement and kidney size at the time of follow-up, outcome and survival. In 55 adults (parents) with ADPKD, the frequency of arterial hypertension syndrome and extrarenal cysts, outcome and survival were analyzed.

It is believed that ADPKD is a disease of adults in most cases, however, according to literature, kidney cysts often occur in childhood, and even in utero [31,49]. According to P. A. Gabow et al. (1997), kidney cysts are detected in 60% of children with ADPKD before the age of 5, and in 75-80% from 5 to 18 years [8]. Our study obtained data that correspond to the literature: in the overwhelming majority (91%) of examined children with ADPKD, cysts in the kidneys were first detected before the age of 15, of which 19.4% were detected very early (before 18 months of age) and only 9% were detected between the ages of 15 and 18. The average age at the time of first detection of cysts in the kidneys was 8.24±0.64 years, the maximum was 16.58 years, and the minimum was 1 month.

We analyzed the characteristics of ADPKD in children at the first detection of cysts in the kidneys.

It is generally accepted that the signs of ADPKD may appear later than the cysts in the kidneys were detected and in most cases the clinical picture develops only in the 3-4 decades of life [19]. However, in our study of 67 children, at the first detection of cysts, clinical (pain syndrome, arterial hypertension) and laboratory (pathology in urine tests) signs of ADPKD were detected in 62.7% of cases. Pain syndrome was diagnosed in 19.4%, changes in urine tests (proteinuria, leukocyturia, erythrocyturia) occurred in 56.7% of children with ADPKD. The literature presents data on the frequency of macrohematuria and proteinuria in children with ADPKD ranging from 10 to 38% [15,20].

Arterial hypertension at the first detection of cysts was found in 3 (4.5%) of 67 children, one of them with mesangioproliferative glomerulonephritis. In the literature, the frequency of arterial hypertension at the first detection of cysts ranges from 6 to 22% [21,30].

Extrarenal manifestations of ADPKD in children are presented in the form of cystic lesions of other organs, valvular anomalies of the heart, vascular pathology, abdominal wall hernias [10,14,18]. Our study confirms this. Extrarenal manifestations of ADPKD at the first detection of cysts were detected in 13.5% of cases and are presented in the form of abdominal wall hernias in 7.5%, mitral valve

prolapse in 4.5% and cysts in the liver in 1.5% of cases.

It is known that in children with ADPKD the kidneys may be unevenly involved in the pathological process, and therefore even in adults under 39 years of age the unilateral location of cysts is considered diagnostically significant [19,23,48]. This is also shown in our work. At the first detection of cysts (mean age 8.24±0.64 years) in 40.3% of children, cysts were located in one kidney, and at the time of follow-up (mean age 13.2±0.54 years) in 4.5%>, unilateral location of cysts was noted.

It should be noted that in our study, unilateral cysts in the follow-up were detected only in children with a 5-year history of the first detection of cysts. In all children with a history of more than 5 years from the moment of detection of cysts, only bilateral location of them in the kidneys was established.

It is known that in children with ADPKD, risk factors for disease progression are multiple cysts in the kidneys (more than 10 cysts by the age of 12), large sizes and, accordingly, increased volume of the kidneys [50]. In this regard, we assessed the number and maximum sizes of cysts, as well as the average length and volume of the kidneys.

The percentage of multiple cysts in our study is lower than that noted in similar (with a similar follow-up period of 5-6 years) studies by foreign authors [35,48]: at the first detection of cysts (14.9% versus 30-38%), at the time of follow-up (41.8% versus 59-81%). It should be noted that in our study, the percentage of children with multiple cysts increases with the years of observation.

The results of the analysis of the features of ADPKD manifestations in children at the time of follow-up (the time from the moment of the first detection of cysts in the kidneys to the moment of follow-up in 67 patients ranged from 1 year to 18 years, on average 5.1±0.6 years) showed that despite the high frequency (62.7%) of clinical and laboratory signs of ADPKD at the first detection, at the time of follow-up 26.9% of children still had no clinical and laboratory signs of the disease. Pain syndrome (41.8%), arterial hypertension (21%) and extrarenal manifestations of ADPKD (31.3%) at the time of follow-up are significantly more

common than at the first detection of cysts (14.9%, 4.5% and 13.5%, respectively).

An assessment of the maximum diameter of kidney cysts and the average length of the kidneys using ultrasound at the first detection of cysts and at the time of follow-up showed significant differences in these values.

For the first time, using regression analysis in children with ADPKD, we established an annual increase in the maximum diameter of cysts in the kidneys according to ultrasound by 0.21 ± 0.03 cm and the average length of the kidneys according to ultrasound by 0.42 ± 0.05 cm. Data on the dynamics of the increase in the diameter of cysts have been published in the literature, but it is difficult to compare the obtained data with the published data, since they were calculated using a different method and represent not an annual increase, but the dynamics of cysts over 1, 3, 5, 10 and 15 years [4]. We did not find similar data on the annual increase in the average length of the kidneys in the literature, so it is difficult to discuss these results.

A comparative analysis of kidney volume in children with ADPKD and healthy children revealed an increase in kidney volume in children with polycystic kidney disease in all age groups, in contrast to healthy children, which corresponds to literature data [11].

The development of arterial hypertension is considered as a formidable predictor of cardiovascular complications of polycystic kidney disease, progressive decrease in renal function. It is known that the development of arterial hypertension before the age of 35 leads to the development of ESRD on average 14 years earlier than with later development [17]. We conducted a comparative assessment of clinical, laboratory and ultrasound signs of ADHS among children with and without arterial hypertension. Reliable differences in the maximum diameter of cysts in the kidneys and in the average length of the kidneys were obtained. Our data are consistent with the results of foreign researchers [17,27].

According to the literature, the third trigger for cystogenesis in ADPKD (the first is a generative mutation in one of the two copies (alleles) of PKD 1 or PKD 2, the second is a somatic mutation of the second "normal" allele) is damage to the

epithelial cells of the tubules, since it initiates the inclusion of reparative processes, that is, rapid growth and division of cells, which, with impaired polycystic function, proceeds excessively actively and ends not with the restoration of the damaged area, but with the development of cysts [37,41]. This may be one of the reasons for the occurrence of new cysts during life in patients with ADPKD, since the likelihood of various obstructive and ischemic injuries increases with age. Our regression analysis showed that the annual increase in kidney length in children with chronic pyelonephritis (0.53±0.06 cm) is significantly greater than in children without pyelonephritis (0.22±0.05 cm), ($p<0.01$). That is, the kidneys in children with pyelonephritis increase in length twice as fast as in children without pyelonephritis. In her work, Kolesnikova IF (2000) showed rapid growth of cysts in children with ADPKD and pyelonephritis. We also obtained a faster increase in the maximum diameter of cysts in children with pyelonephritis (0.24 ± 0.04 cm/year) than in children without pyelonephritis (0.15 ± 0.05 cm/year), but the differences obtained are not reliable ($p>0.05$).

We compared the manifestations of ADPKD in children with very early detection of cysts (n=13) with the rest (n=54) and obtained reliable differences only in the frequency of multiple cysts. The frequency of arterial hypertension and the average length of the kidneys are higher in children with very early detection of cysts, however, the differences obtained are not reliable. No reliable differences were noted in the level of SCF by endogenous clearance and the Schwartz calculation formula, as well as in the maximum size of cysts. A similar study by Shamshirsaz A., RezaBeklieirnia M., Kamgar M. et al . (2005) also showed a significantly higher number of cysts in children with very early detection, however, unlike our work, they also obtained reliable differences in the glomerular filtration rate and the frequency of arterial hypertension [41,49].

We conducted a comparative assessment of the frequency of arterial hypertension, extrarenal cysts in children and parents from families with ADHT.

As a result, a significantly high frequency of arterial hypertension was established in adults (67.3%) compared to children (21%). Our data are consistent

with the data of other researchers [31,38].

According to the literature, extrarenal cysts are less common in children than in adults, but can be detected even in the first year of life [31,35]. Our results confirm this. In adults (parents) with ADPKD, extrarenal cysts are diagnosed significantly more often (52.7%) than in children (9%). In adults, cysts are found in the liver, ovaries, spleen, brain, and testicles. In children, cysts are found in the liver and ovaries. It should be noted that we assessed the frequency of extrarenal cysts based on detection by different imaging methods (ultrasound, CT, MRI). However, in children, cysts in the liver were detected only by CT or MRI; no cysts in the liver were detected by ultrasound. Of the 20 children, CT or MRI revealed liver cysts in 4 (20%), and 0% using ultrasound . Accordingly, CT and MRI are more informative methods for detecting extrarenal cysts in children than ultrasound. This is also indicated by foreign authors [21,27].

There are publications indicating that glomerular hyperfiltration is typical in childhood, which is one of the earliest manifestations of the disease and is associated with a rapid decline in function and an increase in kidney size [17,19]. Our data are comparable with literature data. It was found that the frequency of children with hyperfiltration (SCF>140 ml/min/1.73m") at first detection (29.9%) is higher than at the time of follow-up (17.9%). This is explained by the fact that hyperfiltration is an early sign of changes in kidney function and subsequently these children experience a decrease in SCF.

Impaired concentration and excretory functions of the kidneys according to the Zimnitsky test in children with ADPKD were established both at the first detection of cysts in the kidneys and at the time of follow-up and are presented in the form of hyposthenuria, nocturia and polyuria. At the first detection of cysts, impaired concentration and excretory functions of the kidneys according to the Zimnitsky test were detected in 10.4%, at the time of follow-up in 23.9% of children with ADPKD. According to the literature, a decrease in the concentration ability is a fairly common sign of ADPKD and occurs both in adults and children [51,52]. It is suggested that decreased concentrating ability and increased blood vasopressin

levels may contribute to the development of cysts, hypertension, and progression to TTS [31,36].

Patients with ADPKD may have evidence of distal tubular acidosis. Even with normal GFR, they have a defect in urinary ammonium delivery due to disruption of the corticomedullary structure by the cysts and loss of the corticomedullary concentration gradient. Decreased tubular ammonium excretion leads to a compensatory increase in cortical ammonium production. Increased ammoniogenesis and the resulting metabolic disturbances are thought to contribute to the development of new cysts. Local synthesis of autocoids, cytokines, growth factors, as a result of ammonium-induced activation of complement and inflammation of the renal interstitium, can contribute to abnormal growth of epithelial cells and/or increased secretion of fluid by them [31,40].

In our study, renal tubular metabolic acidosis was diagnosed at the first detection of cysts (14.9%) and at the time of follow-up (19.4%). According to Nishiura J. L., Neves R. F., Eloi S. R. et al. (2009), in adult patients with ADPKD, signs of distal tubular acidosis occur in 7% of cases [34]. We were unable to find data on the frequency of blood acid-base balance disorders in children in the literature, so it is difficult to discuss the obtained results.

Most researchers believe that ADPKD in childhood, taking into account the preserved renal function in terms of the level of SCF, has a favorable course [31,37]. According to Boyer O, GagnadouxMF , GuestGetal . (2007), even with the diagnosis of ADPKD in the prenatal period or on the first day of life, only 2 children out of 26 developed stage IV CKD at an average age of 19 years. However, according to Mekahli D., WoolfAS , Bockenhauer D. (2010) in 39% of cases in children, SCF<90 ml/min/1.73m3" is found. In our follow-up study in children with ADPKD, a decrease in SCF was found at the first detection in 1 child with ADPKD and mesangioproliferative glomerulonephritis (SCF by endogenous creatinine clearance 76 ml/min/1.73m3, according to the Schwartz calculation formula 82 ml/min/1.73m3"), at the time of follow-up in 4 (SCF by endogenous creatinine clearance 30,50,61,72 ml/min/1.73m3", according to the Schwartz

calculation formula 32,55,77,84 ml/min/1.73m3").

Taking into account the fact that one of the criteria for diagnosing CKD is the presence of any markers of irreversible structural changes in the organ, detected once during an intravital morphological study of the organ or during its visualization [17,23], we systematized the SCF data using the Schwartz calculation formula in children with ADPKD, according to the classification of CKD. It was found that in children with ADPKD, stage 1 CKD predominates, at the first detection of cysts (98.5%), at the time of follow-up (94%).

At the first detection of cysts, stage II (SCF 60-89 ml/min/1.73 m2) was established in 1 16-year-old boy with ADPKD and mesangioproliferative glomerulonephritis.

At the time of follow-up (18 and 5 years), stage II CKD (SCF 60-89 in ml/min/1.73 m2) was established in 2 children with very early detection of cysts . Stages III A and III B of CKD were diagnosed in 2 children (16 and 17 years), i.e. kidney damage with moderate and significant decrease in SCF, one of them with a follow-up of 1 year (a boy with glomerulonephritis), the second - with a follow-up of 12 years. The obtained data allow us to assume that the development of glomerulonephritis significantly accelerates the decline in renal function in a patient with ADPKD. It should also be noted that these 2 children with stage III A and III B CKD have arterial hypertension, which confirms the fact that arterial hypertension is a risk factor for earlier decline in renal function in patients with ADPKD [31,38].

The prognosis of ADPKD in children with very early detection of cysts is favorable according to our data, in contrast to those published in the work of Shamshirsaz A., Bekheirnia M. et al. [31]. The authors showed that in 4.3% of cases, children with very early detection develop ESRD by the age of 3.5-4 years. In our study, in 2 children (1.5%) with very early detection of cysts with an average age of 11.5 ± 9.2 years, only a slight decrease in SCF (stage II CKD) was found. Thus, despite the presence in the group of 13 children with very early development of the disease, in 67 children with ADPKD, no fatal outcomes,

terminal renal failure requiring renal replacement therapy, and cardiovascular complications were found. Our results are consistent with literature data [17,34].

In contrast to children, fatal outcomes, development of terminal renal failure and cardiovascular complications were established in adults with ARPKD. Of 55 adults, fatal outcomes were established in 8 (14.5%), of which 5 were from cardiovascular complications (myocardial infarction, cardiac tamponade, hemorrhagic stroke), 3 from terminal renal failure. In 8 patients with ARPKD, cardiovascular complications accounted for 62.5% of the causes of death, and ESRD - 37.5%, which is consistent with the literature data. Cardiovascular complications are a common cause of death in adult patients with ARPKD [31,45]. Of the 55 adult patients with ADPKD, 8 receive renal replacement therapy due to the development of end-stage renal failure. Our study confirms that the prognosis for the course and outcome of adults with ADPKD is serious [47,51].

We calculated the survival of 122 children and parents in families with ADPKD from the moment of first detection of cysts using the moment method of E. Kaplan - P. Meier (1958). According to the data obtained, the probability of survival of 122 children and parents with autosomal dominant polycystic kidney disease from the moment of first detection of cysts was: 5-year - 100%, 10-year - 94%, 15-year - 87%, 20-year - 75%. It should be noted that mortality in the first 10 years from the moment of detection of cysts in patients with ADPKD in our study is due to cardiovascular complications of the disease. We were unable to find data on the survival of patients with ADPKD from the moment of detection of cysts in the literature, so it is not possible to discuss these data.

Thus, as a result of the study of modern diagnostics of autosomal dominant polycystic kidney disease in children and adults, new data were obtained on the characteristics of renal and extrarenal manifestations, course and outcome in children and parents in families with autosomal dominant polycystic kidney disease.

The features of clinical manifestations of ADPKD in children at the time of the first detection of renal cysts and at the time of follow-up were revealed. The

annual increase in cysts and kidney sizes was calculated based on the ultrasound results in children with ADPKD. The features of extrarenal cysts andAHsyndrome in children and parents in families with ADPKD were established. Evaluation of renal function in children with ADPKD by SCF, Zimnitsky test, and blood acid-base balance revealed disturbances in the glomerular filtration rate, concentration and excretion functions of the kidneys, and regulation of acid-base balance. The stages of chronic kidney disease in children with ADPKD were determined depending on the level of glomerular filtration rate using the Schwartz calculation formula, according to the modified National Kidney Foundation classification - K / DOQI. A serious prognosis for the course and outcome of ADPKD in parents of children with ADPKD was confirmed. The probability of survival of children and parents in families with ADPKD from the moment of the first detection of renal cysts using the moment method of E. Kaplan - P. Meier (1958) is shown.

CONCLUSIONS

1. Age-related features of ultrasound diagnostics of renal cysts in children were determined: from 0 to 15 years in 91%, of which from 0 to 18 months (very early detection) in 19.4%; from 15 to 18 years in 9% of cases. The average age of children at the time of detection of cysts by ultrasound (8.24±0.64 years) is significantly lower than that of parents (29.4±1.3 years) in families with ADPKD.

2. In children with ADPKD, bilateral arrangement of renal cysts is prevalent: at first detection (mean age 8.24±0.64 years) in 59.7%, at the time of follow-up (mean age 13.2±0.54 years) in 95.5%, less often - unilateral arrangement (40.3% and 4.5%, respectively). Extrarenal manifestations of ADPKD in children in follow-up (5.1±0.6 years) were established reliably more often (31.3 %) than at the first detection of cysts in the kidneys (13.5%).

3. As a result of regression analysis it was found that the annual increase in kidney length in children with ADPKD who have chronic pyelonephritis is greater than in children who do not have pyelonephritis. The average kidney length and the maximum cyst diameter according to ultrasound in children with ADPKD andAHare significantly greater than in children without AG.

4. The development of arterial hypertension syndrome in families with ADPKD is significantly more frequent in parents (67.2%) than in children (21%). Extrarenal location of cysts is diagnosed significantly more frequently in adults (52.7%), as opposed to children with ADPKD (9%).

6. In children and adolescents with ADPKD, stratification of the severity of chronic kidney disease by SCF revealed a predominance of stage I (94%). In contrast to children, parents with ADPKD were found to develop terminal renal failure (14.5%) and die (14.5%).

7. The probability of survival of children and parents in families with ADPKD, calculated using the method of E. Kaplan - P. Meier (1958), was: 5-year - 100%, 10 - year - 94%, 15-year - 87%, 20-year - 75% from the moment of first detection of cysts.

PRACTICAL RECOMMENDATIONS

1. It is necessary to introduce into nephrological practice international recommendations [8], according to which the criterion of ultrasound diagnostics of ADPKD in individuals with a 50% risk is: in the age group of 15-39 years, detection of 3 or more cysts in the kidneys (unilateral or bilateral), in the group of 40-59 years - 2 or more cysts in both kidneys, in the group over 60 years - 4 or more cysts in both kidneys. For individuals with a 50% risk under 15 years, the presence of large kidneys with high echogenicity, even in the absence of distinct macroscopic cysts on ultrasound, is diagnostically significant.

2. Taking into account the diagnosis of cysts by ultrasound in the kidneys of children with ADPKD up to 15 years of age in 91%, if even 1 cyst is detected in a child under 15 years of age, an ultrasound of the kidneys of all family members should be performed in dynamics, a genealogical analysis with the compilation of a pedigree chart for at least 3 generations.

3. For the purpose of diagnosing extrarenal cysts in children with ADPKD, it is recommended to use more informative methods - MRI/CT.

4. Considering the presence of irreversible structural changes in the kidneys of patients with ADPKD, it is recommended to indicate the stage of CKD (according to the level of SCF in the Schwartz calculation formula) in the diagnosis formulation in accordance with national recommendations [13].

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