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The early onset of Chronic Kidney Disease stage five in 11 years old boy with Autosomal Dominant Polycystic Kidney Disease due to *PKD-1* mutation

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ABSTARCT

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. It usually difficult to detect prior to 30 years of ages with average age onset at 50 years. ADPKD is caused by mutations in one of two genes, *PKD1* and *PKD2*. *PKD1* was associated with more severe disease than *PKD2*, with earlier age at diagnosis, higher number of kidney cysts, the earlier onset of hypertension and faster progression to CKD stage five.

Case: An 11 years old boy diagnosed with CKD stage 5 caused by ADPKD with urinary tract infection. The patient complaint with fatigue, pale, fever, flank pain and cloudy urine. The grandfather had history of renal failure and the aunty had hypertension since she was young. The parents of patient have consanguineous mating. Physical examination found hypertension grade 1 while the laboratory test shown decrease of glomerular filtration rate, anemia, imbalance of electrolyte and metabolic acidosis. Urinary investigation result showed leucosituria and positive for E. Colli. Ultrasonography and CT stonography showed bilateral multiple cysts in the kidneys with left kidney enlargement. His parents also got multiple cysts in both of kidneys with the normal size kidneys. Genetic analysis showed homozygous for missense mutations 11734insC, in exon 43 of the *PKD1* gene. The patient got regular hemodialysis and other supportive therapy.

Conclusion: The early onset of CKD stage five in ADPKD is related to *PKD1* homozygous gene mutation, male gender and enlargement of kidney.

Keywords: Autosomal dominant polycystic kidney disease, chronic kidney disease, PKD 1 mutation, early onset.
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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent life threatening hereditary disease that causes small, fluid filled cysts to develop in the kidneys. It is affecting from 1 in 500 to 1 in 1000 individuals worldwide. Although ADPKD often considered as disease of adults, it is clear that the disease begins in childhood.[1] It accounts for approximately 5% of chronic kidney disease stage 5 in adults, while very rarely found in children.[2]

Approximately 85% of ADPKD cases are caused by mutations in the *PKD1* gene, which is located on chromosome 16, while the remaining cases are due to mutations in *PKD2* located on chromosome 4.[3] *PKD1* mutation is associated with more severe disease than *PKD2*, with earlier age at diagnosis, higher number of cyst, earlier onset of hypertension and faster progression to CKD stage 5.[4] Affected children may develop any of the renal symptoms associated with enlarge kidney. In contrast with adult patients, most affected children have few or no symptoms.[5,6]

The diagnosis of polycystic kidney disease is usually established by ultrasonography, which reveals diffuse hyperechogenicity, enlarged kidney and, in most children, cysts are usually but not always bilateral.[5] Affected patient typically present with multiple cysts bilaterally and a positive family history consistent with autosomal dominant inheritance. Molecular genetic testing is available for ADPKD and maybe useful for evaluation of individuals at risk with equivocal imaging results, younger at-risk individuals as a living-related kidney donor, and individuals with atypical or *de novo* renal.[3] Treatment for ADPKD is directed at reducing morbidity and mortality due to complications of the disease and includes management of hypertension, renal insufficiency, and end stage renal disease.[2]

We present a rare case about chronic kidney disease stage 5 in 11 years old boy with autosomal dominant polycystic kidney disease due to *PKD1* mutation.

CASE REPORT

An 11 years old boy, referred from S regency hospital diagnosed with CKD stage 5 and hypertension stage 1. In the beginning, the patient feels fatigue since a month prior to hospitalization. Paleness had been realized by the parents since the patient in 10 years old with the patient looked pale in both

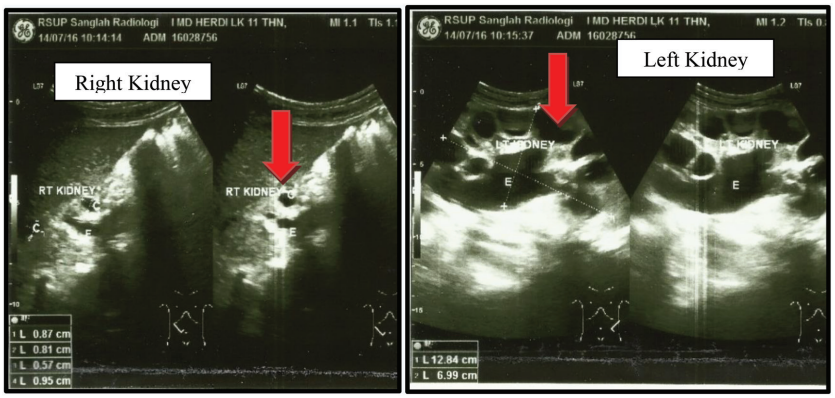

Figure 1 USG imaging showing bilateral multiple cysts in right and left kidney

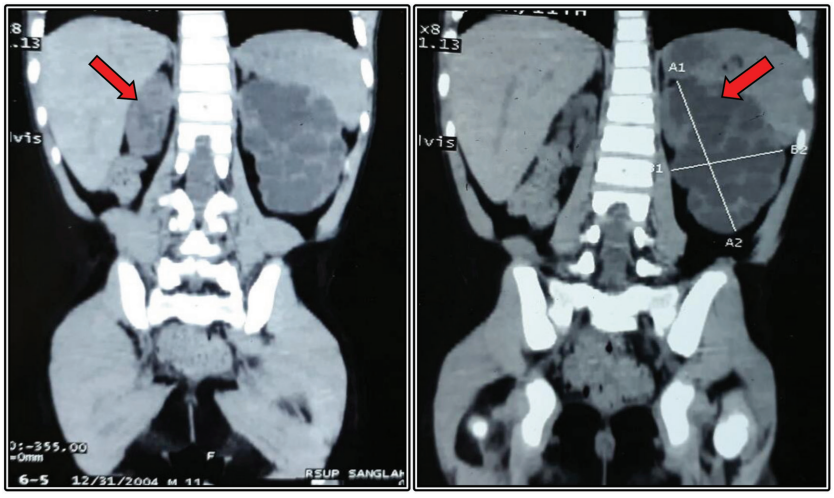

Figure 2 CT Stonography showing bilateral multiple renal cysts and enlargement of the left kidney

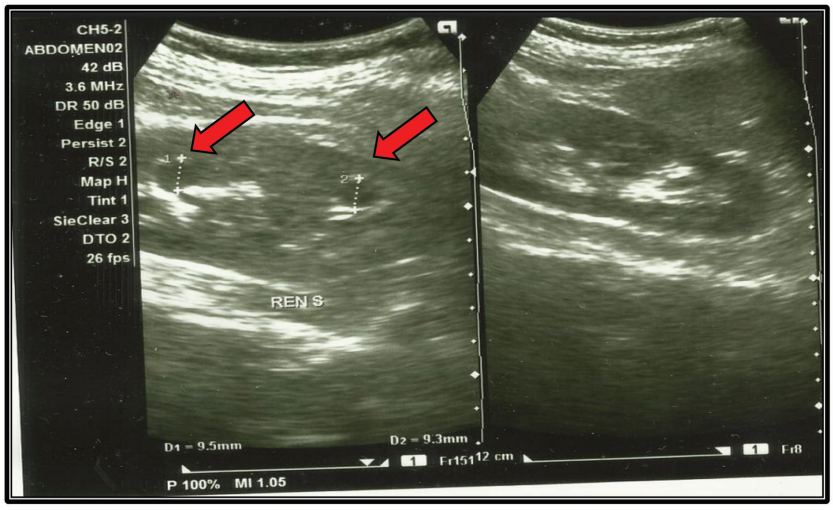

Figure 3 USG imaging of the mother's renal reveal small multiple renal cysts

eyes, both of hands and foots. The paleness last about a month before hospitalized. The urine was said to appear cloudy since the patient aged 5 years old, fluctuate and sometimes accompanied by flank pain. At the time of admission, the patient urinates well with no pain, but the urine is still cloudy. He got fever since 2 weeks prior to hospitalization which said to get better by paracetamol administration.

From the patient's past history, the patient was hospitalized once when he was 5 years old in the regency hospital because of cloudy urine and pain. Afterward, each time he got the same complains, the patient always visit the general doctor and had been suggested not to consume excessive amount of calcium containing food.

From the family history, the patient is the second son from the two children in the family. His older sister was 19 years old and in good health. His aunty (from mother's line) got hypertension since she was young and the grandfather (from mother's line) passed away because of renal failure, caused by unknown etiology. There was no history of chronic disease in the parents like hypertension and renal failure, but they have consanguinous mating.

When in S hospital, the patient had the high blood presure and had been administered with furosemid and captopril. Renal function test evaluation found high evel of BUN and Creatinin. Then, the patient was reffered to Sanglah hospital.

During physical examination, the patient was alert. The blood pressure was 100/60 mmHg (among 50-90 percentile) and the other vital sign was normal. He got pales conjunctivae in the eyes and pain on left of costovertebral angle. There was no edema in both of palpebras or foot and no palpable mass in the abdomen. According to CDC 2000 growth chart, the patient was under nutrition and stunted.

The laboratory investigation showed moderate anemia with Hb 6,6 g/dL; MCV 85,96 fL; MCH 25,6 pg dan MCHC 31,11 g/dL. There was an electrolyte imbalance with natrium 129 mmol/L; kalium 6,09 mmol/L; klorida 99,9 mmol/L; kalsium 7,93 mg/dL. The examination of the kidneys function revealed blood urea nitrogen (BUN) at 172 mg/dL, creatinin 13,03 mg/dL and GFR 4,93 mL/ minute/1,73 m^2. The blood gas analysis showed metabolic acidosis with pH 7,03; pCO2 9,8 mmHg; pO2 186,2 mmHg; BE -28 mmol/L and HCO3- 2,6 mmol/L. From urinalysis examination, macroscopic evaluation showed that the urine was cloudy in colour; protein +2; leukocyte +2. Microscopic evaluation showed erythrocyte at 5-10; full leukocyte; and epitel 6-8. Electrocardiography examination showed that there was tall T wave. The patient diagnosed by CKD stage 5, hypertension stage 1, moderate normocromic normositer anemia, suspected for urinary tract infection, undernutrition and stunted. Patient got hemodialysis with packed red cell tranfusion on hemodialysis,

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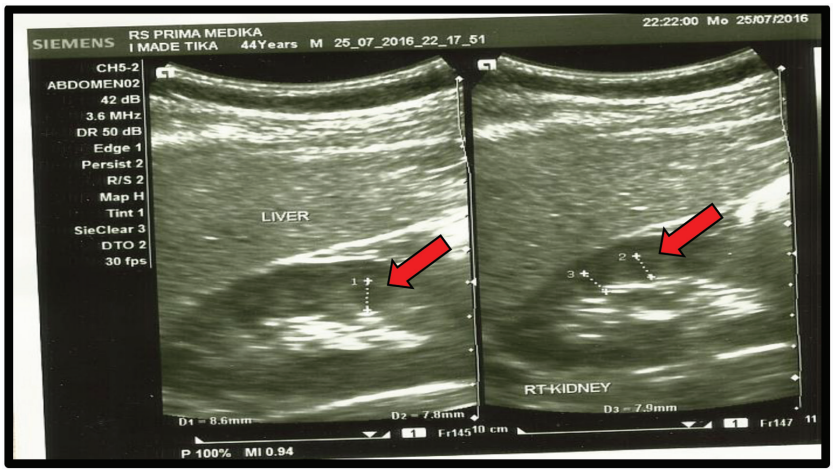

Figure 4 USG imaging of the patient's father's kidneys also shows small multiple renal cysts

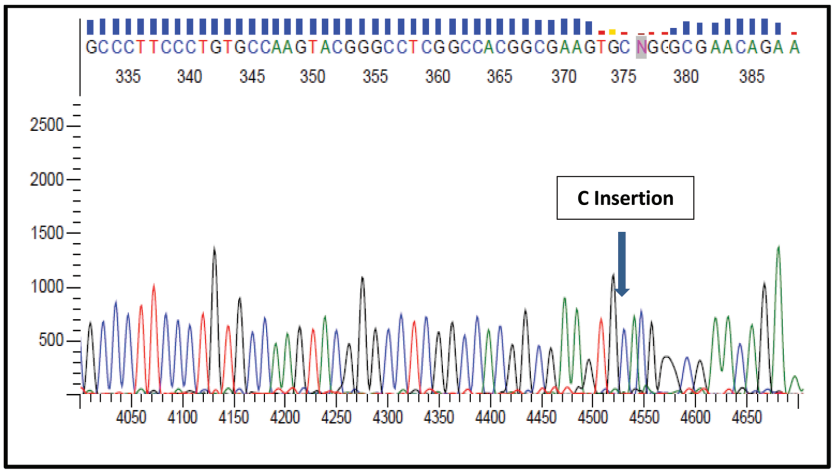

Figure 5 Frame shift mutations (c insertion) in exon 43 of the PKD 1 gene

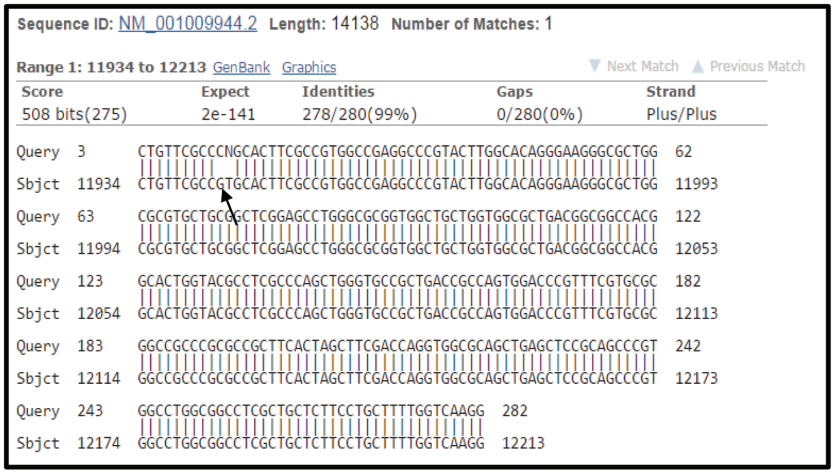

Figure 6 Frame shift mutations (c insertion) in exon 43 of the PKD 1 gene

administration of furosemid and captopril as antihypertension and ceftriaxone. Further supportive examinations were conducted using USG and urine culture.

On the 4th days of hospitalization, the patient got seizure with blood presure at 146/103 mmHg (above 99 percentile). The patient was diagnosed with hypertensive crisis and had been given sublingual nifedipine and antiseizure. The dossage of antihypertensive was increased following the seizure.

USG examination revealed bilateral multiple cysts in kidneys, moderate hydronephrosis in left kidney, mild hydronephrosis in right kidney and enlargement of left kidney. The right kidney has 8,21 cm length while left kidney has 12,84 cm. There is no renal or urinary tract stone (Figure 1). Urin culture examination found bacteria *E Colli* at 10^5 CFU/ml which confirmed the diagnosis of urinary tract infection and the ceftriaxone was continued for 7 days.

The patient has been consulted to the departement of urologic surgery to manage the cysts on the kidney. From the surgeon perspective, the therapy can only be achieved through transplantation. But this procedure still could not be conducted in Bali yet so the supportive therapies were given. The CT stonography examination was conducted to evaluate the presence of stone in kidney and urinary tract. The result of CT scan did not show a stone in the kidney or urinary tract. There was hydronephrosis grade 4 in the left kidney with multiple cysts in both of the kidneys. There was no sign of extrarenal cysts (e.g hepatic cyst) (Figure 2).

To evaluate the hereditary aspect of the disease, the parents were also examined using abdominal USG. The USG examination showed few cysts in their kidneys with no clinical symptoms (Figure 3 and 4). The parents Renal function was also evaluated. The Mother's patient showed decrease of GFR (66,1 ml/minute/1,73 m^2) and the father's patient also showed decrease of GFR (64,68 ml/ minute/1,73 m^2). The case indicated that the patient's polycystic kidneys disease is autosomally dominant. Afterward, DNA analysis was conducted in both patients and his parents to evaluate any mutation in *PKD1* gene.

The patient also evaluated for calcium, PTH, fosfat, vitamin D level, serum iron, TIBC and ferritin before discharged from hospital. Vitamin D 25-OH level was found at 12,1 ng/ml, calsium level was 7,42 mg/dL, PTH level was 634 pg/ml, fosfat level was 3,9 mg/dL, serum iron was 170 µg/dL, TIBC was 209 µg/dL and feritin was 492,7 ng/ml. The patient got oral calcium, vitamin D suplementation and planned for erythropoietin injection. Pasien was suggested for continous ambulatory peritonial dialysis (CAPD) but the parent rejected it and still prefer hemodyalisis. The patient had been discharged from hospital with the controlled blood pressure by antihypertensive agent and regular

hemodialysis for twice a week. The GFR at the time of discharge was 9,5 mL/minute/1,73 m^2.

The genetic report was arrived two months after the sample collection. The test methodology was analyzing the coding and flanking intronic regions of the *PKD1* (NM_001009944.2) genes perfomed by Big Dye Terminator (Applied Biosystems). Sequencing analysis showed homozygous for frameshift (missense) mutations 11734insC, in exon 43 of the PKD 1 gene (Figure 5 and 6). This mutation was predicted to be pathogenic and played important role in patient's condition. The parent's genetic analysis was also conducted but not yet finished.

Based on clinical manifestation, family history, imaging finding and genetic examination, it was concluded the cause of CKD stage 5 in this case was ADPKD.

DISCUSSION

Autosomal dominan polycystic kidney disease (ADPKD) is the most common inherited kidney disease, occurring at an incidence of approximately 1: 1000. As its name implies, it is inherited as an autosomal dominant trait. However, there is considerable phenotypic variability even within the same family. Males and females are affected equally and ADPKD is present in all races and ethnicities.[2] Typically, only a few renal cysts are detected in most affected individuals before 30 year of age and only 2% of patients with ADPKD present with early clinical manifestations before 15 years old.[6,7] The diagnosed in childhood are often discovered to have renal cysts incidentally while undergoing an imaging study for other indication. Alternatively, they may be diagnosed as part of an evaluation for gross hematuria or hypertension. Additional signs and symptom prompting evaluation and diagnosis can include urinary tract infection or urolitithiasis. Flank pain from enlarging kidneys or cysts hemorrhage is typically not a presenting symptom in children. It accounts for approximately 5% of CKD stage 5 in adults, while it is a very rarely found in children.[2,8,9] In this case, the patient is 11 years old with early manifestation of ADPKD. The patient presented with complains like fatigue, paleness, high blood pressure and decrease of GFR (4,93 mL/ minute/1,73 m2). Those conditions are apparently similar with the description of CKD stage 5. The patients also had the signs of urinary tract infection like fever, cloudy urine and positive result of urine culture. The intermitent flank pain experienced by patient was probably caused by the enlargement of the kidney.

Ultrasonography is the most common imaging modality used to diagnose ADPKD. As with affected adults, the typical ultrasonographic appearance of ADPKD in children is the presence of renal cysts. It is not uncommon for children to show asymmetric involvement or event isolated unilateral cysts.[2] In adult at 50% risk for ADPKD (i.e those with an affected parent), spesific diagnostic ultrasonography criteria have been established. The "Ravine criteria", which were recently update are used to diagnosis ADPKD based on the number of cysts in each kidney at certain ages (table 1). However, no such criteria have been developed for at risk children.[10,11] Because simple cysts are rare in children, the finding of even one cyst in patient at risk for ADPKD is considered diagnostic by some.[2]

Renal enlargement is a universal and unique characteristic of ADPKD.[3] Older children have larger and more numerous renal cysts and develop progressive renal enlargement, whereas patients with acquired cystic kidney disease will have a limited number of cysts in kidneys that are reduced or of normal size that are echogenic with a thin cortex.[3] Unlike the tubular cysts in autosomal recessive polycystic kidney (ARPKD), the cysts in ADPKD are round. Multiple or discrete cysts of varyng size may be scattered throughtout the cortex, including the subscapular location, because cyst in ADPKD can arise from anywhere in the nephron or collecting system.[11,13] The finding of another cyst in the liver or pancreas indicates the diagnosis of ADPKD, although these are infrequently found at initial presentation in children.[7] Extra kidney cysts can be found most often in the liver, pancreas, spleen, thyroid and arachnoid membranes. Despite the fact that ADPKD is a systemic disease involving multiple organs, pediatric patients often do not exhibit extra renal signs or symptoms, although these have been reported in children even at a very young age.[2,9] In those younger individuals where ultrasound might yield equivocal or indeterminant

Table 1 **Performance characteristic of ultrasound diagnostic criteria for individual who are born with 50% risk for PKD1[6,12]**

Age (yr)	Diagnostic Criteria	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
15-29	At least two renal cysts (unilateral or bilateral)	Approximately 96	100	Approximately 97	100
30-59	At least two cysts in each kidney	100	100	100	100
60 or older	Four or more cysts in each kidney	100	100	100	100

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results, both computed tomography (CT) scan and magnestic resonance imaging (MRI), with and without contrast enhancement have been used for diagnosis of ADPKD.[6] In this case, USG showed multiple cysts in his both of kidneys (more than two cysts in each kidney). The size of left kidney has length 12,84 cm (above 95 percentile based on age). CT stonography showed bilateral multiple cysts in kidneys by the enlargement of the left kidney. The extrarenal cyst like hepar cysts did not find. The result of USG from both of parents showed bilateral few cysts in their kidneys without clinical symptoms.

Although ultrasound imaging may be an adequate diagnostic tool in at risk individuals older than 30 years old, this modality may not be sufficiently sensitive in younger individual or for those from families who have milder disease. DNA based assay maybe indicated in certain clinical situations were imaging cannot provide a definitive clinical diagnosis.[1] ADPKD is caused by mutations in one of two genes, PKD 1 (chromosome 16p13.3) which encodes polycystin-1 (PC1) and PKD 2 (chromosome 4q21) which encodes polycystin-2 (PC2). PC1, PC2 and other proteins associated with renal cystic disease have been localized to the primary cilium in the renal tubule and other epithelium. The cilium may function as a flow detector, facilitating calcium influx when flow is present and restricting influx in response to a lack of flow or loss of the PC complex. In this manner, multiple signaling pathways that regulate cell proliferation and fluid secretion, including cyclic adenosine monophosphate (cAMP), are altered in favor of cysts formation.[14] Among adult patients referred for nephrology evaluation, PKD1 mutations account for approximately 78% of cases with the remaining 13% of cases due to PKD2 mutations and 9% due to denovo mutations.[9] Approximately 200 different PKD1 and >50 PKD2 mutations have been reported, with most of them predicted to truncate the mutant protein (as result of frameshift deletions and insertions, nonsense mutations, or splice defect).[6] In this case, showed homozygous for frameshift mutations 11734insC, in exon 43 of the PKD 1 gene. Genetic screening for the presence of mutation in the PKD 2 was not done because of possible mutations in this genes are very small and cost consideration are quite expensive.

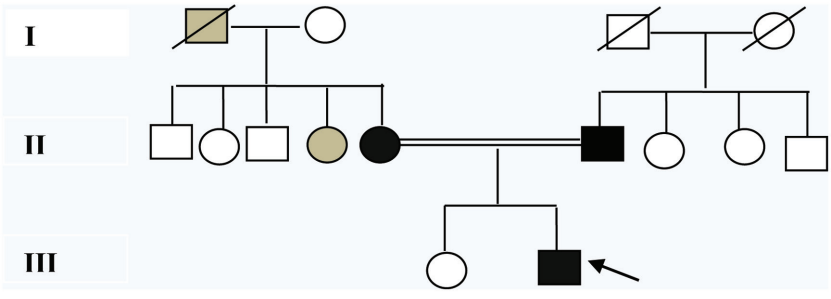

Figure 7 Family tree (pedigree) of the patient

ADPKD is the most common Mendelian disorder of the kidney. In autosomal dominant disorder, the mutated gene is a dominant gene located on one of the nonsex chromosomes (autosomes). In a person with an autosomal dominant disorder has a 50 percent chance of having an affected child with one mutated gene (dominant gene) and a 50 percent chance of having an unaffected child with two normal genes. In pedigree analysis, the main clues for identifying an autosomal dominant disorder are that the phenotype tends to appear in every generation of the pedigree.[15] In this case, the pedigree showed the phenotype tends to appear in second and third generation. In first generation, grandfather's patient passed away caused by chronic kidney disease with unknown etiology. His aunty got hypertension caused by unknown etiology (figure 7). Other family member never had USG examination to detect asymptomatic cyst. Patient's sibling refuse to do the USG and gene examination.

The natural course of ADPKD varies significantly, with onset of CKD stage 5 reported from childhood to age > 80 years, and median age of 58 years was reported recently for PKD1, which is much more common than PKD2. Rapid ADPKD progression may be defined as onset of CKD stage 5 at age <55 years, development of CKD stage 3 at < 40 years old, onset of hypertension < 18 years old, presence of total kidney volume greater than that expected for a given age, or presence of multiple complication. There are many factor that may predict and/or effect ADPKD disease progression. These factors include PKD1 mutation (particulary truncating mutation), men, early onset of hypertension, early and frequent gross hematuria, large kidneys and among women, three or more pregnancies.[16,17] In this case, patient with a diagnosis ADPKD and has experience CKD stage 5 in 11 years old. The onset of CKD stage 5 should earlier caused by the patient has predictor factor like male gender, mutation of PKD 1 gene like truncating mutation (*frameshift* mutation) and enlargement of left kidney.

Some data suggests that those individuals with milder disease courses may have incompletely penetrant *PKD1* alleles, indicating that the level of functional PKD1 protein may be important for cyst initiation. There is also some suggestion that the patients who inherit ADPKD from their father tend to experience less severe disease, compared to maternally inherited one. Patient with heterozygous mutations of both *PKD1* and *PKD2* experience worse outcomes and more severe disease than those with either mutation alone, and the homozygous of *PKD1* mutation is thought to be lethal in utero.[18]

In this case, the patient inherit ADPKD from his mother and father. From the gene analysis, patient had homozygous *PKD1* mutation and still alive until now but had early onset of CKD stage 5.

The Treatment of ADPKD in this case not only included antibiotics and antihypertensive but also renal replacement therapy. The patient had been experiencing the complication of CKD stage 5 and has been undergoing regular hemodialysis two times a week. Parents prefer hemodialysis therapy to peritoneal dialysis, because it was directly conducted by health personnel. Dialysis is a common means of renal replacement therapy for patients with ADPKD awaiting kidney transplant. Options for ADPKD patients include both hemodialysis and peritoneal dialysis, though the latter is commonly thought to lead to poor outcomes due to concerns of abdominal wall complications, including leaks and intestinal perforation, in part due to increased intra-abdominal pressure resulting from large kidney volumes. Increased intra-abdominal pressure may cause some difficulties in peritoneal dialysis. Hemodialysis has also been shown to be an effective and safe means of renal replacement in ADPKD patients.[18]

The prognosis of children ADPKD can be varies from one to another. Approximately 50% of patient with ADPKD will progress to CKD stage 5, although the age at which this occurs varies.[2] In this case, patient had CKD stage 5 with complication in the age of eleventh and getting the regular hemodialysis. We searched for evidence and found a study entitled with "***Long term survival of children with end stage renal disease"*** *by* McDonald SP, Craig JP, *The New England Journal of Medicine,* 2004;350 (26):2654-2662 *(valid, important and applicable, level of evidence 2B, grade of recommendation B).* The conclusion of this journal that the children start to get hemodialysis when they are 10-14 years had 5- years survival rate about 88%, 79% survival in 10 years, 70% survival in 15 yeras, and 68% survival in 20 years.

CONCLUSION

The natural course of ADPKD varies significantly; the average age at onset of chronic kidney disease (CKD) was 50 years. There are many factors that may predict and/or affect ADPKD disease progression. These factors include *PKD1* mutation (particularly truncating mutation), male gender, early onset of hypertension, early and frequent gross hematuria, large kidneys and among women, three or more pregnancies. The early onset of CKD stage 5 in this case may be explained by several aforementioned factors like male gender, homozygous mutation of *PKD1* gene and enlargement of left kidney.

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