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Tolvaptan ameliorated kidney function for one old autosomal dominant polycystic kidney disease patient: A case report

Zhou L *et al.* Tolvaptan ameliorated kidney function of ADPKD

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Abstract

BACKGROUND

Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous cysts within the kidneys. Disease progress of some patients often occurs at the early stage. Thus, managing and controlling disease progress is important to slow the kidney function decline especially for the patient with other disorders.

CASE SUMMARY

One 80-year-old male autosomal dominant polycystic kidney disease (ADPKD) patient with chronic kidney disease and other clinical disorders was treated with Tolvaptan and Edoxaban. Estimated glomerular filtration rate (eGFR), creatinine (CR) and uric acid (UA) were monitored during the treatment. In addition, the whole exome sequencing was performed to screen ADPKD genetic variants. The kidney function decline was prevented after using Tolvaptan and Edoxaban treatment, in the meantime, venous thromboembolism (VTE) was removed, and leg and pedal edema were alleviated. One mutation c.10102G>A /p.D3368N in PKD1 gene was identified.

CONCLUSION

Tolvaptan combined with Edoxaban administration could delay kidney function decline and eliminate the edema caused by the thromboembolism.

Key Words: Chronic kidney disease; Autosomal dominant polycystic kidney disease; Deep vein thrombosis; Tolvaptan; Case report

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Core Tip: Autosomal dominant polycystic kidney disease is a genetic and heritable kidney disease. It appears with cyst formation and growth, kidney enlargement and eventually leads to the end stage renal disease. Some patients with severe polycystic kidney disease and the end stage kidney disease have been treated with nephrectomy and early dialysis therapy, however, the life quality of these autosomal dominant polycystic kidney disease (ADPKD) patients declines due to the above treatment. In this case report, Tolvaptan combined with Edoxaban administration improved kidney function for one old ADPKD patient while avoiding the decreased life quality from nephrectomy or dialysis therapy.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic and heritable kidney disease. This disease appears cyst formation and growth, kidney enlargement and eventually leads to the end stage renal disease. Most cases are caused by the heterozygosity of the pathogenic variant PKD1 or PKD2^[1]. In addition, heterozygosity of variants in GANAB and DNAJB11 were also reported to cause autosomal dominant polycystic kidney disease in 0.3% and 0.1% of families, respectively^[2,3]. However, the molecular mechanisms underlying the renal dysfunction resulted from mutations in ADPKD genes are still unclear and needs to be further investigated.

Some patients with severe polycystic kidney disease and the end stage kidney disease have been treated with nephrectomy and early dialysis therapy. However, nephrectomy has a high risk due to refractory hypotension because of post-operative loss of renin secretion^[4]. The life quality of the ADPKD patients declines due to restraint time and access surgery for dialysis therapy. The surgery and the dialysis treatment also add the medical expenses for the patients and their family^[5]. Therefore, delayed initiation of dialysis in chronic kidney disease (CKD) patients is thought meaningful. It is critical to choose and determine appropriate administration strategy for patients with aggressive progress kidney disease to prevent kidney function decline and complication occurrence.

Tolvaptan (TLV) is an oral selective arginine vasopressin type V2 receptor antagonist that has shown to an ability to slow the rapidly progressing polycystic kidney disease, and has been approved to treat ADPKD in the European Union, Japan, South Korea, Canada, and US^[6]. The efficacy of Tolvaptan has been reported for patients with CKD in other studies^[7,8]. Recently, the administration of Tolvaptan also demonstrated that it decreased the worsening of renal function^[9,10]. Furthermore, Tolvaptan therapy was more effective in maintaining renal function than treatment with increasing doses of loop diuretics because Tolvaptan has strong diuretic effect. It can reduce edema, and won't destroy the blood electrolyte balance^[11,12]. In this case report, one old male ADPKD patient who had been diagnosed chronic kidney disease with other complications including venous thromboembolism was treated with Tolvaptan. Considering the patient had leg edema plus venous thrombosis of the lower extremities, Edoxaban was also used to administer this patient since Edoxaban could reduce thromboembolism in the patient with chronic kidney disease as an oral anticoagulant^[13]. Follow up therapeutic results of this patient demonstrated that the combined administration of Tolvaptan and Edoxaban could improve kidney function for this old patient, and reduce edema accompanied with venous thromboembolism disappearance.

CASE PRESENTATION

Chief complaints

One 80-year-old, male autosomal dominant polycystic kidney disease patient with leg edema and pedal edema presented at China-Japan Friendship Hospital in Nov. 2020.

History of present illness

The patient had a distended abdomen accompanied by leg edema and pedal edema. He had chronic kidney disease.

History of past illness

This patient had 14 years of cerebral infarction, 30 years of polycystic kidney disease, and 20 years of hypertension. In addition, this patient had other clinical disorders, renal anemia, hyperlipidemia, arteriosclerosis obliterans, lacunar infarction, and type 2 diabetes.

Personal and family history

This patient had ADPKD. One family member, the patient's daughter was included in this case report study for the whole exome sequencing in order to screen the ADPKD genetic variants.

Physical examination

This patient's body weight was 62.5 kg and his height was 170 cm. Blood pressure was 140/80 mmHg. The distended abdomen was observed, and leg edema and pedal edema were also found.

Laboratory examinations

eGFR was calculated according to CKD-EPI creatinine equation^[14]. Hemoglobin (HGB), albumin, and total protein were examined. Liver function and kidney function were evaluated by measuring alanine aminotransferase (ALT), aspartate transaminase (AST),

creatinine (CR), and uric acid (UA). Coagulation-associated molecules, such as fibrinogen (FIB), D-dimer (D-D), fibrin degradation product (FDP) were measured. All clinical laboratory examinations were performed and data were recorded before the start of treatment and in every month after the treatment.

Imaging examinations

Computed tomography (CT) and abdominal ultrasound were performed on this patient, and the kidney size and multiple cysts were measured (Figure 1). Venous thrombosis of the lower extremities was also examined by ultrasound (Figure 2).

Whole exome sequencing

Peripheral blood of this patient and one family member were collected for the whole exome sequencing analysis to screen ADPKD associated single nucleotide polymorphism (SNP), Insertion/Deletion (In/Del), and copy number variation (CNV). Genomic DNA was extracted using DNA extraction kit. Library was prepared by using reagents from KAPA Biosystems Inc. (Wilmington, MA, USA). Hybridization capture was completed by using IDT whole exome capture kit by Fulgent Company (Beijing, China). The whole exome sequencing was run on Illumina Novaseq 6000 sequencer (San Diego, CA, USA). FastQ data were processed and sequencing reads were aligned to human genome hg19/GRCh37 using BWA (Burrow-Wheeler Aligner). Then, variants SNP/InDel were identified with SAMtools. Candidate SNP/InDel was further screened. The genetic mutations (SNP/InDel) were predicted as harmful by SIFT, Polyphen-2_HVAR, and MutationTaster, and referring to HGMD, OMIM, ClinVar, UCSC, Ensembl, RefGene database as well. SNP/InDel variants were classified into pathogenic and likely pathogenic ones according to the criteria and guidelines of American College of Medical Genetics and Genomics (ACMG).

FINAL DIAGNOSIS

The final diagnosis was chronic kidney dysfunction and accompanied by venous thrombosis of the lower extremities.

TREATMENT

Tolvaptan was used as a diuretic to enhance the ability of the kidneys to process water. In the meantime, Edoxaban was used as an oral anticoagulant to treat venous thrombosis to alleviate the lower extremity edema and pedal edema. Besides Tolvaptan and Edoxaban, Roxadustat was used to treat anemia and other medicines were also administered to cure other diseases.

The doses of Tolvaptan and Edoxaban were adjusted according to the clinical symptoms and the corresponding administration strategy. At the treatment initiation, 7.5 mg of Tolvaptan and 15 mg of Edoxaban were daily used. In the second month, Edoxaban dosage was increased to 30 mg daily due to new venous thrombosis formation. After that, 30 mg of Edoxaban was the daily maintenance dose without change. At the beginning of the third month, Tolvaptan dosage was adjusted to 15 mg per day because the creatinine level was still high. Five months later, kidney function tended to be stable, the edema and the thrombosis also disappeared. Tolvaptan dosage was increased to restrict the growth of cysts. Tolvaptan was used twice per day, 15 mg in the morning and 7.5 mg in the evening. After one year, Tolvaptan was administered twice per day, 15 mg each time.

OUTCOME AND FOLLOW-UP

Patient health condition

After the combination treatment of Tolvaptan and Edoxaban, the patient's health status was improved. Total protein, albumin, and HGB were within normal range and renal anemia had been cured. The bilateral lower extremity edema disappeared. So far, this patient has been followed up for 15 mo.

Whole exome sequencing result

Sequencing data was about 10G, and the average sequencing depth was 140X. Based on the whole exome sequencing data of this patient and one family member, one mutation was found for the gene PKD1 (NM_001009944.2) c.10102G>A /p.D3368N. According to the ACMG Criteria and Guidelines for variant analysis, this genetic variant has been recorded in the HGMD database, and the frequency of this variant in the GnomAD database is 0.000250 (63/251880). MutationTaster predicted that this variant may be harmful, while Polyphen-2_HVAR and SIFT predicted it is not a harmful variant, and this variant was defined as a variant of uncertain significance (VUS). All variants defined as VUS were shown in Table 1. Raw data is available *via* <https://www.biosino.org/download/node/data/OED732748>.

Imaging results

CT imaging demonstrated a relatively small chest and a distended abdomen, with massively enlarged kidneys, shown in Figure 1A. Multiple cysts were observed within bilateral kidneys, representative imaging shown in Figure 1B. The abdominal ultrasound also showed the enlarged echogenic kidney with multiple cysts, right kidney size is 19.2 cm x 13.8 cm x 12.0 cm, and left kidney size is 21.8 cm x 12.8 cm x 12.7 cm. The largest cyst on right kidney is 6.8 cm x 5.2 cm, the largest cyst on left kidney is 10.1 cm x 2.7 cm, as shown in Figure 1C and 1D. Venous thrombosis of the lower extremities was observed, shown in Figure 2A and 2B, leg edema and pedal edema were attributed to the obstructed venous return. The thrombosis disappeared after a few months of treatment, shown in Figure 2C and D.

Therapeutic effect

After the patient was administered with Tolvaptan and Edoxaban for 3 mo, the venous thrombosis in lower extremities was removed as shown in Figure 2C and D. The estimated glomerular filtration rate was raised from 14.43 to 31.25 (mL/min/1.73 m²), which is shown in Figure 3A. Creatinine and uric acid were obviously reduced shown in Figure 3B and 3C. In addition, hemoglobin was increased compared with the

beginning of treatment, which meant the renal anemia was relieved, and the data was shown in Figure 3D.

DISCUSSION

Autosomal dominant polycystic kidney disease is one ¹ common monogenic disease causing the end stage renal failure, occurring in 1:400 to 1:1,000 individuals worldwide. It is difficult to estimate the precise prevalence for ADPKD because its progression rate and severity vary among the patients^[15]. The cysts compress and destroy the kidney tissue resulting in a progressive loss of function in a few decades. About 50% of patients at the age of 60 to 70 progress the end stage kidney disease^[16]. For the patients with the end stage kidney disease, kidney transplantation is a good therapeutic option to improve the quality of life. Since the incidence of renal cancer of the polycystic kidney disease patients is higher when comparing with the healthy population, it would be important to make tumor screening for PKD patients. Moreover, there is a potential risk of transmission of cancer from donor to recipient^[17]. Thus, it may be necessary to obtain and estimate the donor history when performing kidney transplantation for the patient with ESRD.

In this case report, the patient has 30 years of autosomal dominant polycystic kidney disease with chronic kidney disease. According to the whole exome sequencing result, only c.10102G>A /p.D3368N variant on PKD1 and c.4009G>A/p.D1337N on PKHD1 were identified as variants of uncertain significance. However, whether they are potentially pathogenic is unclear because one family member of this patient with the same variants does not have polycystic kidney disease. The kidney function examination results indicated there was acute kidney injury with higher creatinine and uric acid, moreover server leg and pedal edema were also observed. The edema was usually managed with furosemide, however, taking this medicine may lead to kidney overload and further impair renal function. Since Tolvaptan has been approved as a diuretic drug to combat hyponatraemia and slow kidney function decline, Tolvaptan was used to treat this patient to protect kidney against further damage.

Tolvaptan was started at 7.5 mg per day. Water intake was limited at 1.5 to 2 liters per day. Because of hypernatremia concern, the Tolvaptan dose was slowly increased to 15 mg. Serum sodium and potassium were consistently within normal range. Because Tolvaptan may cause liver damage side effect^[18], the liver function was evaluated by measuring ALT and AST, both of them were within normal range during treatment. At the beginning of treatment, serum creatinine concentration was remarkably exceeding normal range, indicating acute kidney injury occurrence. After 3 mo of Tolvaptan administration, creatinine had fallen to half level of the treatment initiation and decreased to normal range after 15 mo.

Estimated glomerular filtration rate is one important indicator for realistic reflection of kidney function, and is most commonly used for determining stages for chronic kidney disease^[19]. eGFR was less than 15 mL/min/1.73 m² at the treatment initiation, demonstrating this patient was at Stage 5 of chronic kidney disease, according to National Kidney Foundation developed criteria, Kidney Disease Outcomes Quality Initiative (NKF KDOQITM)^[20]. After 15 mo, eGFR increased to 37.32 mL/min/1.73 m² which is within eGFR range at Stage 3 of chronic kidney disease. Thus, after Tolvaptan treatment, the kidney function of this patient was recovered and protected against further injury, though kidney size and cyst size had no obvious change according to the ultrasound results, which may indicate that the increased Tolvaptan could limit the cyst growth. Kidney size and cyst size are unlikely to get smaller as this old patient has longer ADPKD history, which usually makes the kidney and cyst enlargement irreversible. For this old patient, preserving residual renal function (RRF) is an important aim. The loop diuretic furosemide is typically used in the treatment of heart failure and chronic kidney disease, but reducing RRF is often observed^[21]. Thus, Tolvaptan has advantage over furosemide to administer this old patient with almost ESRD.

Ultrasound examination on bilateral legs showed right tibial and peroneal venous thrombosis and right lower extremity atherosclerosis with plaque formation at the beginning of treatment, which was attributed to obstruct venous return led to the

edema. In the meantime, Edoxaban was started at 15 mg per day to treat venous embolism, and adjusted dose based on the embolus size and the patient's condition. After the patient took Tolvaptan and Edoxaban for a few months, the blood flow in the deep veins of bilateral lower extremities run smoothly, and no obvious thrombosis was found in the deep veins of bilateral lower extremities by ultrasound examination. The leg and pedal edemas disappeared. Edoxaban exhibits several advantages for the treatment and prevention of venous thromboembolism^[22,23]. Especially, it exhibited safety and efficacy when used to treat over 80 year old patient with poor renal function. The patient recovered from chronic kidney disease, and his condition became better.

CONCLUSION

In this case report, the patient was administered with Tolvaptan and Edoxaban for 15 mo, his kidney function decline was delayed, his acute kidney injury was recovered, kidney failure was prevented, and a dialysis therapy was avoided. The life quality of the patient was maintained and the aggressive progress of chronic kidney disease to the end stage of kidney disease was prevented. Tolvaptan was safe and effective to slow CKD progress when it was used to treat this old ADPKD patient with chronic kidney dysfunction and deep vein thrombosis in the legs. Therefore, Tolvaptan could be useful for old ADPKD patients to protect kidney disease progress and alleviate complications.

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