Epidemiological estimates and early detection of polycystic kidney disease by ultrasonographic assessment in Japan

Minoru Kobayashi¹, Takao Kamai²

¹Department of Urology, Utsunomiya Memorial Hospital, Utsunomiya, ²Department of Urology, Dokkyo Medical University, Mibu, Tochigi, Japan

Abstract

Aims: To estimate the prevalence of autosomal dominant polycystic kidney disease (ADPKD) and provide the evaluation of new ultrasonographic criteria and clinical indicators to help its early detection. Materials and methods: A total of 30750 individuals for health check-up with abdominal ultrasonography (US) were included, in which 231 suspects of ADPKD based on the number of renal cysts were extracted. They were divided into 4 groups by the grade of suspicion (definitive, a strong suspect, a fair suspect and a weak suspect). Longitudinal data of US and renal function tests were compared between the groups. The estimated prevalence rate was 0.068% from the study subjects. The level of eGFR did not differ between the definitive and suspects, while the annual estimated glomerular filtration ratio (eGFR) decline was significantly larger in the former (p<0.001). The subjects with growing renal cysts showed a larger annual eGFR decline than those without growth (p=0.0324). The proposed cut-off set at the first quartile of the annualized eGFR change efficiently divided the subjects according to the presence of cyst growth (p= 0.027) and the grade of suspicion of ADPKD (p=0.028). Conclusion: The prevalence rate of ADPKD was higher than the corresponding rate previously reported in Japan (0.025%), suggesting that health check-ups may be an efficient opportunity to pick up undiagnosed ADPKD. The large annual eGFR decline and the presence of growing cysts may be feasible indicators to isolate ADPKD and should be introduced into US based screening to facilitate early detection of ADPKD.

Keywords: autosomal dominant polycystic kidney disease; health check-up; ultrasonography; estimated glomerular filtration ratio; prevalence

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease, nearly half of which develops into end-stage renal disease by late middle age [1-3]. In addition, ADPKD harbors systemic disorders involving multiple organs such as extra-renal cysts (liver, pancreas, spleen, seminal vesicle and arachnoid membrane), cardiac valvular defects, colonic diverticulosis and cerebral aneurysm [4-6]. Particularly, ADPKD patients had up to a 5-fold higher risk for rupture compared with the general population [7]. In Japan, more than 31000 ADPKD patients have been diagnosed, accounting for 3% of patients on dialysis (https://www.nanbyou.or.jp/entry/295). ADPKD has emerged as a promising therapeutic target among intractable rare diseases since tolvaptan, vasopressin receptor antagonist, was approved for the treatment of ADPKD in Japan, being the first country in the world to do so in 2014. Tolvaptan has reduced the rate of kidney volume growth and kidney function decline [8-10]. Owing to such advances in pharmacological management, ADPKD gained great attention in terms of early detection and sustained follow-up. Detection of the characteristic cystic renal involvement by imaging modalities is the first key to diagnosis of ADPKD. Ultrasonography (US) has become the preferred diagnostic imaging method since it is sensitive, widely accessible and inexpensive without the use of radiation or contrast material. Herein, we proposed the new
ultrasonographic criteria and some clinical features of the subjects with multiple cysts in both kidneys as possible candidates for ADPKD. Subsequently, we surveyed subjects undergoing health check-ups including US at our hospital to access the prevalence of ADPKD as a current status and epidemiological information of ADPK.

Material and methods

We surveyed a total of 30750 individuals who underwent health check-up with abdominal US between April 2019 and March 2020. According to the Evidence-based clinical practice guidelines for Polycystic kidney disease (PKD) 2020 [11], its diagnosis is based on familial incidence and findings of renal cysts obtained by computed tomography (CT), magnetic resonance imaging (MRI) and USS (table I). Based on US findings and clinical (urolithiasis, hypertension and cerebral bleeding) and family history (cerebral bleeding, hemodialysis, renal transplantation and ADPKD) as indicated in Table II, possible subjects for ADPKD were categorized into 4 groups: a weak suspicion, a fair suspicion, a strong suspicion and definitive ADPKD. Those in the former 3 groups as ADPKD suspects were also divided into 2 groups according to changes in the cyst growth: increase in either maximal size, number or both (with cyst growth) and no increase in maximal size and number (without cyst growth). Determination of estimated glomerular filtration ratio (eGFR) was made with the use of the Chronic Kidney Disease Epidemiology Collaboration equation [12]. The slope of the change in eGFR was determined using the latest as baseline and previous (2 to 3 years before) values with adjustment for the duration of the observations and with interpolation to 1 year, denoted as the ΔeGFR/y. US was performed using the Xario 200 system (Cannon Medical Systems, Tochigi, Japan) with convex probe PVU-375BT 2-5MHz. We obtained prior approval from the institutional review board (#21-004) and informed consent of all patients according to the World Medical Association Declaration of Helsinki, revised in 2000.

Statistical analysis

As all the obtained data did not exhibit normal distribution, data were expressed as median (interquartile

Table I. Diagnostic criteria of ADPKD [11]

| Criteria | Details |
|----------|---------|
| When familial incidence is confirmed | 1) Presence of 3 or more cysts is confirmed in each kidney by ultrasonography.  
2) Presence of 5 or more cysts is confirmed in each kidney by CT or MRI. |
| When familial incidence is not confirmed | 1) Presence of 3 or more cysts is confirmed in each kidney by CT, MRI, or ultrasonography in subjects aged 15 or younger and the following diseases are excluded.  
2) Presence of 5 or more cysts is confirmed in each kidney by CT, MRI, or ultrasonography in subjects aged 16 or older and the following diseases are excluded. |
| Diseases to be excluded | Multiple simple renal cyst  
Renal tubular acidosis  
Multicystic kidney (Multicystic dysplastic kidney)  
Multilocular cysts of the kidney  
Medullary cystic disease of the kidney (Juvenile nephronophthisis)  
Acquired cystic disease of the kidney  
Autosomal recessive polycystic kidney disease |

Table II. Classification of the possible subjects for ADPKD

| Classification | Details |
|----------------|---------|
| ADPK suspects: | 1) weak suspicion: ≥ 3 cysts in both kidneys and <5 in at least one kidney  
2) fair suspicion: ≥ 5 cysts in both kidneys  
3) strong suspicion: ≥ 5 cysts in both kidneys and ≥ 2 items of the following conditions:  
• clinical (urolithiasis, hypertension, and cerebral bleeding) and family history (cerebral bleeding, hemodialysis, renal transplantation, and ADPKD)  
• showing increase in size or number of cysts  
eGFR < 60ml/min/1.73mm² |
| Definitive ADPKD: | enlarged both kidneys with a majority of parenchyma replaced by multiple cysts |
The Mann-Whitney U-test was used to test differences between the two groups. Differences among 3 or more groups were tested by the Kruskal-Wallis test, supplemented by the Mann-Whitney U-test with Bonferroni adjustment as post-hoc analysis. The proportion of the number of cases was compared using Fisher’s exact test. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the free R statistical software (version 3.2.2, https://cran.r-project.org/).

**Results**

Of all the subjects, 1924 (6.26%) subjects were noted to have cysts in both kidneys, of which 231 (0.0032%) had ≥3 cysts in both kidneys that would meet the diagnostic criteria in terms of the number of renal cysts. We focused on these subjects as the ADPKD candidates and their demographics were shown in Table III. Most of them (227/231, 98.3%) repeatedly underwent annual health check-up with USG for a long period (median 3311, range 336-6241 days). They were categorized into 4 groups: a weak suspicion (148, 64.1%), a fair suspicion (30, 13%), a strong suspicion (32, 13.8%) and definitive ADPKD (21, 9.1%). Based on these results and the size of population in this study, the prevalence rate of definitive ADPK patients was 6.8 per 10,000 population (0.068%). If 32 subjects with a strong suspicion were assumed to be affected, the estimated prevalence rate would increase up to 17.2 per 10,000 population (0.172%).

In order to characterize kidney function for ADPK suspects, age, eGFR and annual eGFR change were compared among the above-mentioned groups. There were significant differences in the latest and previous eGFR among the 4 groups by the Kruskal-Wallis test (p<0.001 and 0.002, respectively). The post-hoc Kruskal-Wallis test showed that both eGFR levels in a strong suspicion group were significantly lower than those in weak and fair suspicion groups, while the annual eGFR decline was significantly greater in a definitive ADPK group compared with the other 3 groups comprising older subjects than the former.

Next, we investigated whether the eGFR slope was affected by cyst growth in ADPKD suspects. The annualized eGFR decrease was significantly larger in those with cyst growth than those without cyst growth (p=0.0324) (fig 2).

Lastly, in an attempt to set a feasible cut-off value to discriminate those who were likely to develop ADPKD, the subjects were dichotomized into the large de-
crease group and the small decrease group in the annualized eGFR change according to the first quartile value of the $\Delta eGFR/y$ (-3.46 ml/min/1.73m$^2$/y). Needless to say, a greater annual eGFR decline was seen in the large decrease group [5.38 (-6.98 – -4.48) ml/min/1.73m$^2$/y] compared with the small decrease group [-0.34 (-1.73 – 1.05) ml/min/1.73m$^2$/y] (p<0.001). We compared the case distribution according to the presence of cyst growth and the amount of decrease in the $\Delta eGFR/y$ using this cut-off value. The subjects without cyst growth more frequently showed a small decrease in eGFR, while those with cyst growth were more liable to experience greater deterioration in kidney function represented by the $\Delta eGFR/y$ (p=0.027 by the Fisher’s exact test) (fig 3a). Likewise, the proportion of the number of cases according to the amount of annualized decrease in eGFR was compared among the grade of suspicion of ADPKD. The frequency of large annualized decrease in eGFR was proportional to the grade of suspicion of ADPKD, with a weak suspicion group being the least and a strong suspicion group being the most liable to have large annualized decrease in eGFR ($p = 0.028$ by the Fisher’s exact test) (fig 3b).

**Discussion**

The advent of the vasopressin V$_2$ receptor antagonist tolvaptan that addresses the underlying pathophysiology of ADPKD has dramatically changed the essence of treatment from palliative to curative intent, reduced in the kidney volume and the decline in the eGFR [8-10]. In this context it is important to estimated current prevalence of ADPKD to better understand the exact burden of ADPKD. However, estimating ADPKD prevalence at population level is challenging because a significant fraction of patients are asymptomatic and undiagnosed. In addition, high costs of genetic testing and diagnostic imaging such as CT and MRI limit the feasibility of screening in general population. As a result, this disease progress over decades and leads to a clinically detectable decline in kidney function typically presenting at the fourth decade of life [13]. On the other hand, according to the aforementioned Japanese guideline [11], the diagnosis of ADPKD does not require genetic testing but depends on diagnostic imaging based on the number of renal cysts detected by US as well as CT and MRI. Such a clinically accessible diagnostic approach allowed us to estimate the prevalence rate of ADPKD in the general population undergoing health check-up, yielding the prevalence rate of 6.8 per 10,000. A previous Japan-
European meta-analysis of population-based epidemiological studies yielded an average prevalence of 2.7 per 10,000 (95% CI = 0.73–4.67) and a point prevalence of 3.63 per 10,000 in the province of Modena (Italy) [16]. The feasibility of using patient claims data to estimate the diagnosed prevalence of ADPKD was reported with the rate of 4.3 per 10,000 in the US, which provides support for this method because of the consistent results between claims data and national data sources [17]. As a new approach to estimate the prevalence of ADPKD, the population-based whole-genome sequencing provided a higher prevalence of ADPKD associated mutations of 9.3 cases per 10,000 sequenced [18]. Collectively, our US diagnosed prevalence estimate of 6.8 per 10,000 together with the above-mentioned study with similar subjects for health check-up seems higher than those mostly found in the population-based epidemiological studies. Moreover, the ultimate prevalence rate is likely to be even higher as there may be potential candidates for ADPKD in suspicious groups in the present study.

If the family history is unclear, its diagnosis is liable to be indefinite in most cases as long as kidney enlargement is absent, although larger benefit may be expected if tolvaptan treatment is started earlier. To encourage early diagnosis and treatment intervention, we attempted to find additional indices to US findings indicative of ADPKD. We categorized the subjects into 3 grades of suspicion (weak, fair, and strong) based on the number of cysts and the assumed risk factors as shown in Table I. The levels of eGFR were significantly lower in a strong suspicion group compared with the other 2 groups of ADPKD suspects. Although definitive ADPKD showed the same levels of eGFR as ADPKD suspects, the annualized decrease in eGFR was significantly larger in definitive ADPKD than the others. Younger age in ADPKD patients could compensate a larger annualized decrease in eGFR values at similar levels to the others. Therefore, the annualized eGFR change may be a more reliable indicator of kidney function independent of age for renal cystic disorders. We also demonstrated that a larger annualized decrease in eGFR was seen in those with growing cysts in comparison with its counterpart, while the annualized eGFR change did not differ with the roughly categorized number of cysts (3-4 or ≥5 used in grade of suspicion), implying that the ΔeGFR/y well reflects a dynamic change of renal morphology and function, the essential feature of ADPKD.

In ADPKD patients, kidney function may remain within the normal range until the age of 40 to 60 years, making eGFR measurement less useful in monitoring the disease in its early stages. At the point that eGFR decline has started, morphological changes in the kidneys are visible on imaging studies, exhibiting notably enlarged with little recognizable parenchyma. At this stage, the average rate of GFR decline is 4-6 ml/min per year [19]. Thus, it is necessary to establish a reliable indicator to determine who will develop definitive ADPKD among its suspects. We identified the first quartile value of the annualized eGFR change (-3.46 ml/min/1.73m²/y) as a possible discriminator of projected end-stage renal disease (ESRD). When dichotomized by this threshold, the subjects with a large annual decline in eGFR more frequently belonged to the group with growing cysts and a strong suspicion of ADPKD. Indeed, this value is close to the reported first quartile value of the annual eGFR slope (-3.1 ml/min/1.73m²/y) for Asians in the retrospective study to examine racial difference in eGFR decline, ESRD, and mortality through an integrated health system [20]. Thus, the subjects in a strong suspicion group with a higher chance to show large decline in annual eGFR slope may have the highest likelihood of ADPKD. Those with a large annualized decrease in eGFR in the other two groups, who are less frequent but more in absolute numbers, are also unignorable candidates of ADPKD and may need close follow-up.

We should note a couple of limitations of the present study. First, we did not faithfully follow the diagnostic criteria of ADPKD according to the guideline but proposed an original criterion to pick up ADPKD suspects as a screening method on daily practice in general health check-ups aiming at middle-age and elderly people. Second, our questionnaire is not specifically prepared to isolate ADPKD suspects and lacks the medical history of complications of ADPKD including colonic diverticula, cerebral aneurysm, and mitral regurgitation as long as they are asymptomatic to be unexamined. Third, we did not measure kidney size routinely unless obvious kidney enlargement was seen. It has been reported that total kidney volume continuously increases by an average of 5.5% per year throughout the course of ADPKD [8], and that the long diameter of the kidney was well correlated with measured volume by MRI [21]. Although measurement of kidney volume by US is inaccurate, the long diameter of the kidney may be an effective surrogate indicator to monitor and prognosticate early stages of ADPKD. These flaws should be amended to enhance diagnostic significance of health check-ups for the subjects having kidney enlargement with cystic formation.
Conclusions

The prevalence rate of ADPKD obtained using the proposed criteria in the present study (6.8: 10,000) was at least 2.6 folds higher than the rate in the recent meta-analysis of European countries, but the same frequency as the recent Japanese study conducted in similar subjects for health check-ups, suggesting that such screening intervention may provide a better chance to pick up undiagnosed ADPKD. The large annual eGFR decline and growing cysts may be useful indicators to identify ADPKD in those with multiple cysts in both kidneys. Introducing these criteria into US based screening during health check-up may facilitate efficient detection of ADPKD and allow early introduction of therapeutic agents such as tolvaptan to delay its progression to ESRD.

Conflict of interest: none

Acknowledgement: We are grateful to the daily efforts of the staff performing ultrasonographic examinations at the center for health check-ups in our hospital.

References

1. Grantham JJ, Mulamalla S, Swenson-Fields KJ. Why kidneys fail in autosomal dominant polycystic kidney disease. Nat Rev Nephrol. 2011;7:556-566.

2. Pippia M, Kramer A, Noordzij M, et al. The European Renal Association–European Dialysis and Transplant Association Registry Annual Report 2014: a summary. Clin Kidney J 2017;10:154–169.

3. Spithoven EM, Kramer A, Meijer E, et al. Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. Kidney Int 2014;86:1244–1252.

4. Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. J Am Soc Nephrol 2002;13:2384-2398.

5. Chapman AB, Devuyyst O, Eckardt KU, et al. Autosomal dominant polycystic kidney disease (ADPKD): executive summary from a kidney disease: improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2015;88:17-27.

6. Hogan MC, Abebe K, Torres VE, et al. Liver involvement in early autosomal-dominant polycystic kidney disease. Clin Gastroenterol Hepatol 2015;13:155–164.e6.

7. Sanchis IM, Shukoor S, Irazabal MV, et al. Presymptomatic Screening for Intracranial Aneurysms in Patients with Autosomal Dominant Polycystic Kidney Disease. Clin J Am Soc Nephrol 2019;14:1151-1160.

8. Torres VE, Chapman AB, Devuyyst O, et al; TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407-2418.

9. Torres VE, Meijer E, Bae KT, et al. Rationale and design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3-4 Study. Am J Kidney Dis 2011;57:692–699.

10. Muto S, Okada T, Yasuda M, Tsubouchi H, Nakajima K, Horie S. Long-term safety profile of tolvaptan in autosomal dominant polycystic kidney disease patients: TEMPO Extension Japan Trial. Drug Healthc Patient Saf 2017;25:93-104.

11. Research Group on Intractable Kidney Diseases: Diagnostic criteria for ADPKD. Evidence-based guidelines for the diagnosis of polycystic kidney disease (PKD) 2020. Tokyo Igakusha, Tokyo; 2020.

12. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-612.

13. Blanchette CM, Liang C, Lubeck DP, et al. Progression of autosomal dominant kidney disease: measurement of the stage transitions of chronic kidney disease. Drugs Context 2015;4:212275.

14. Higashihara E, Nutaheara K, Kojima M, et al. Prevalence and renal prognosis of diagnosed autosomal dominant polycystic kidney disease in Japan. Ningen Dock International 2019;6:62-68.

15. Solazzo A, Testa F, Giovanella S, et al. The prevalence of autosomal dominant polycystic kidney disease (ADPKD): A meta-analysis of European literature and prevalence evaluation in the Italian province of Modena suggest that ADPKD is a rare and undiagnosed condition. PLoS One 2018;13:e0190430.

16. Willey C, Kamat S, Stellhorn R, Blais J. Analysis of Nationwide Data to Determine the Incidence and Diagnosed Prevalence of Autosomal Dominant Polycystic Kidney Disease in the USA: 2013-2015. Kidney Dis (Basel) 2019;5:107-117.

17. Lanktree MB, Haghighi A, Guiard E, et al. Prevalence Estimates of Polycystic Kidney and Liver Disease by Population Sequencing. J Am Soc Nephrol 2018;29:2593-2600.

18. Klahr S, Breyer JA, Beck GJ, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol 1995;5:2037-2047.

19. Derose SF, Rutkowski MP, Crooks PW, et al. Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system. Am J Kidney Dis 2013;62:236-244.

20. Bhutani H, Smith V, Rahbari-Oskou F, et al; CRISP Investigators. A comparison of ultrasound and magnetic resonance imaging shows that kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. Kidney Int 2015;88:146-151.