
Article:
Cadnapaphornchai, M.A. and Ong, A.C.M. orcid.org/0000-0002-7211-5400 (2023) Hypertension in young adults with autosomal dominant polycystic kidney disease: a case for early screening? Clinical Kidney Journal, 16 (6). pp. 901-904. ISSN 2048-8505

https://doi.org/10.1093/ckj/sfad049

Clinical Kidney Journal, 2023, vol. 0, no. 0, 1–4

https://doi.org/10.1093/ckj/sfad049
Advance Access Publication Date: 16 March 2023
Editorial Comment

EDITORIAL COMMENT

Hypertension in young adults with autosomal dominant polycystic kidney disease: a case for early screening?

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ABSTRACT

ADPKD is the most common hereditary kidney disease and a major cause of kidney failure world-wide. Significant kidney enlargement occurs decades preceding loss of kidney function. However, the earliest clinical manifestations of disease have been less well characterized in young adults, a typically healthy population who do not often seek routine medical care. In this study, Martinez and colleagues report a high prevalence of hypertension among young adults (18–30 years) enrolled in the Spanish ADPKD registry REPQRAD. Their findings confirm previous studies in children and young adults with ADPKD and make a strong case for earlier screening and intervention within this age group.

Keywords: ADPKD, age, ambulatory blood pressure monitoring, cardiovascular, hypertension

ADPKD is the most common hereditary kidney disease, affecting 1 in 1000 individuals. It is characterized by the progressive development of kidney cysts with associated compression of local kidney parenchyma eventually leading to fibrosis and kidney dysfunction, such that ∼50% of affected individuals will reach kidney failure by 60 years of age. In the current era, recognition that severe structural kidney disease is occurring decades in advance of kidney dysfunction has redirected attention to the importance of interventions that affect total kidney volume (TKV) early in the course of the disease, including recent clinical trials in children and young adults with ADPKD targeted specifically towards diminishing the rate of kidney cyst growth [1–3]. However, clinical manifestations and disease risk have been less well characterized in young adults, a typically healthy population who may not seek routine medical care.

In this issue of CKJ, Martinez *et al.* report clinical findings in 346 young adults (18–30 years) enrolled in the Spanish ADPKD registry REPQRAD. Within the entire registry cohort ($n = 2580$, mean age 50.5 years), the frequency of hypertension increased with age with an overall prevalence of 46% and male predominance (52 vs female 43%, $P < 0.001$). In the young adult subgroup, hypertension affected nearly 17% of participants between 18 and 24 years of age and 37% of participants aged 25–30 years. Similar to the overall registry population, young adults showed a lower prevalence of hypertension in females although when present, hypertension was initially documented at a similar mean age

Received: 21.12.2022; Editorial decision: 9.3.2023

of 21 years in both genders. Kidney enlargement was evident but kidney function was well preserved. Within this young adult cohort, hypertension was associated with increased severity of ADPKD including a *PKD1* gene variant, family history of early onset kidney replacement therapy, lower eGFR, larger kidney size, and history of haematuria, features that have been identified previously as risk factors for ADPKD progression [4, 5]. Nearly 40% of the cohort had liver cysts while 3.5% had intracranial aneurysms, supporting the systemic nature of ADPKD even at a young age.

Martinez *et al.*'s findings are in agreement with those previously published in a US study of Caucasian patients with ADPKD. Kelleher *et al.* described the characteristics of hypertension in 516 individuals with ADPKD, aged between 1 to 55 years, with normal serum creatinine and no proteinuria, who were followed up between 1985 and 2000 [6]. Of the 516 participants with ADPKD, 37% had hypertension. The frequency of hypertension similarly increased with age with a male predominance (46 vs female 30%, $P < 0.0005$). The young adult (20–34 years) subgroup demonstrated a particularly high occurrence of hypertension compared to the general age-matched population (49 vs 7% [7]). Interestingly, in the ADPKD cohort overall, hypertensive women were more likely to receive antihypertensive medication and to demonstrate controlled blood pressure than hypertensive men. The higher frequency of hypertension in young adults in the Kelleher *et al.* group compared to Martinez *et al.* group is likely to have been influenced by selection bias as a tertiary referral centre focusing on PKD research versus a national clinical registry. Nonetheless, both studies support a significant risk of hypertension in younger patients with ADPKD.

Children with ADPKD can present with many of the same clinical manifestations as older patients, although impaired kidney function and intracranial aneurysm are rare findings. Normal blood pressure in childhood differs between males and females and increases with age and height. In contrast to adult medicine where the definition of hypertension is based on clinical outcomes, norms for blood pressure in childhood are defined statistically and are based on large population-based studies of healthy children, with hypertension defined as blood pressure at or above the 95th percentile for age, gender, and height, or blood pressure ≥130/80 for adolescents who are 13 years of age and older [8, 9]. Paediatric clinical trials in ADPKD therefore classify participants based on this statistical definition and not solely on the basis of having been prescribed renin angiotensin blockade [10–12, 2, 13–16, 1, 17, 18]. It is unlikely that large-scale high-quality studies to establish the relationship between childhood blood pressure and adult cardiovascular and kidney disease risk will ever be performed, either in ADPKD or in the general paediatric population. Optimal studies in this regard would require decades-long longitudinal study, ideally with randomized controlled trials comparing screening versus no screening and treatment versus no treatment [19]. Limitations to successful study include potential loss to follow up over decades-long study periods and long-term funding considerations. However, supportive evidence from studies in the general paediatric population demonstrate tracking of blood pressure from childhood to adulthood and suggest that elevated blood pressure in childhood may initiate chronic cardiovascular dysfunction (including increased left ventricular mass index, vascular endothelial dysregulation, and premature atherosclerosis) in later adult life [20, 21]. In longitudinally studied cohorts of children who develop hypertension as adults, there are strong associations between blood pressure and adiposity at 10 years of age as well as lipid and glucose status at 16 years of age [22]. The Bogalusa heart study also showed that over a 36-year follow up, the current percentile cut-points used to define paediatric hypertension correlated with risk estimates for the subsequent development of intermediate markers of adult cardiovascular disease such as LVH and metabolic syndrome [23]. Both the American Academy of Pediatrics [9] and the European Society of Hypertension [24], among others, recommend the screening and treatment of childhood hypertension as defined.

With these background considerations, the prevalence of hypertension in children with ADPKD has been reported to range from 20 to 40% with increasing frequency with age during childhood [25, 26]. As noted by Martinez *et al.*, this is likely to be an overestimate of the true prevalence of hypertension in affected children, as there are likely to be many children whose ADPKD remains silent and undiagnosed. Nevertheless, the presence of hypertension in younger patients with ADPKD is a finding of concern. High TKV is an important surrogate marker for eventual loss of kidney function. In children and young adults with ADPKD, hypertension correlates well with TKV by both ultrasound (Fig. 1 A) and MRI throughout the range of blood pressure [2, 16]; indeed, an early decline in eGFR can already be observed in young hypertensive individuals with ADPKD (Fig. 1 B). There is also a significant correlation between left ventricular mass index and TKV throughout the range of normal and elevated blood pressure in children and young adults with ADPKD [12]. Children with blood pressure in the high normal range (75–95th percentile for age, height, and gender, with hypertension defined as ≥95th percentile) demonstrate left ventricular mass index comparable to that of hypertensive children with ADPKD and significantly higher than that of children with ADPKD and blood pressure below the 75th percentile [12]. Similar to older adults with ADPKD, children and young adults with ADPKD show evidence of vascular dysfunction, including impaired endothelium-dependent dilation (EDD) and stiffening of the large elastic arteries [17]. In adults with ADPKD, hypertension has been shown to further impair EDD and pulse wave velocity compared to adults with ADPKD and normal blood pressure and to adults with essential hypertension [27]. The risk to developing hypertension over time is significant in children and young adults. In one study of children and young adults with ADPKD, 52% of participants with baseline blood pressure in the high normal range (75–95th percentile) and 28% with baseline blood pressure below the 75th percentile but with >10 kidney cysts developed hypertension over a 5-year study period [2].

With advances in kidney replacement therapy, the most frequent cause of mortality in ADPKD is cardiovascular disease. Given these concerns, it is imperative that we closely follow young individuals who have or are at-risk for ADPKD. In children with ADPKD, 24 h ambulatory blood pressure monitoring (ABPM) has been shown to be a valuable tool. Using ABPM, 35% of children with ADPKD can be shown to have a lack of nocturnal blood pressure dipping [28] and 18% demonstrate isolated nocturnal hypertension [26], an important predictor of target organ damage [29]. Although fewer studies have been conducted in young adults with ADPKD, ABPM has value for detection of masked hypertension in this group [30].

Considering the association between blood pressure elevation above the 75th percentile and TKV [2, 16] or LVMI [12] in children and young adults with ADPKD , as well as the long-term implications of these factors on progression in ADPKD specifically [31–33] and cardiovascular disease in general, there is rationale to treat blood pressure elevation in children and young adults with ADPKD. Most antihypertensives are well tolerated

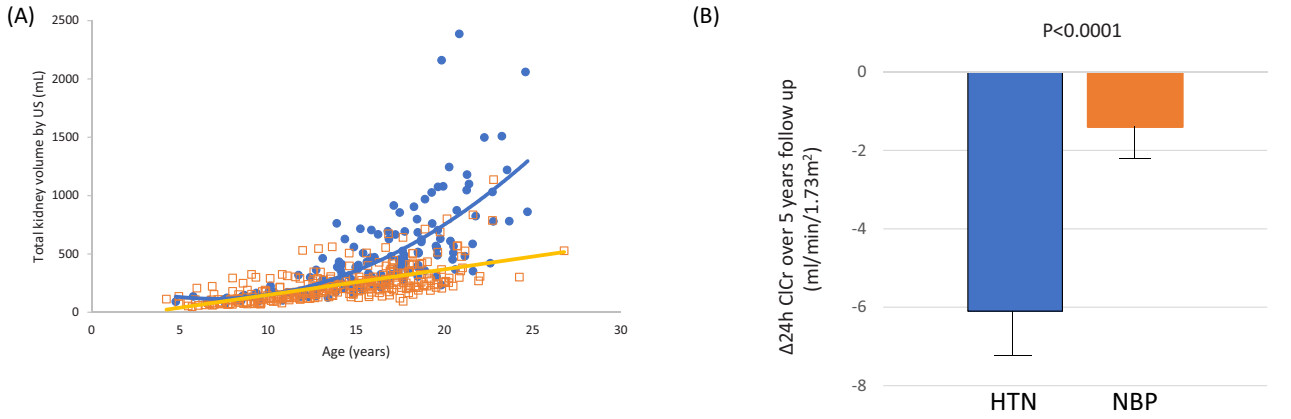

Figure 1: The relationship between hypertension, TKV and kidney function decline in children and young adults with ADPKD. (**A**) A more rapid increase in TKV measured by ultrasound (US) with age occurs in individuals with hypertension as compared to those with normal blood pressure. (**B**) Hypertensive young individuals show significantly greater decline in annualized eGFR over 5 years' follow up, as assessed by 24-hour urine creatinine clearance (CrCl), compared to those with normal blood pressure (HTN, hypertension, shown in blue. NBP, normal blood pressure, shown in orange). Figure adapted from [2].

although they can have side effects that may occasionally be serious. Blood pressure lowering should therefore focus on high-risk patients within the context of shared decision making with parent(s)/guardian(s) and the patient as developmentally appropriate.

The strength of this retrospective cross-sectional study is the potential large national dataset derived from 36 Spanish kidney units for longitudinal studies. Its major weakness is the likely selection bias in recruitment from secondary or tertiary care similar to previously reported paediatric studies. Data on completeness of recruitment of eligible patients at individual centres and differences in the recruitment rate between centres were not provided. Of those recruited, only 98/346 (28%) were genotyped, 216/346 (63%) had ultrasound reports, and 110/346 (32%) had MRI as predictive markers significantly limiting their discriminating value for disease severity within the cohort. Further characterization of risk with respect to extrarenal manifestations including hepatic cysts and intracranial aneurysms was limited. Martinez *et al.*'s findings suggest these may be important manifestations in early adulthood yet more rigorous assessment is required: in this study, liver cystic burden was not quantified and the criteria for aneurysm screening were not stated.

Young adults often view themselves as generally healthy and without need for routine medical care. However, important manifestations of ADPKD can affect the child and young adult [34]. Hypertension in particular is an early feature of ADPKD which confers significant long-term cardiovascular and kidney risk; studies like HALT-PKD suggest that some long-term risk can be mitigated by antihypertensive therapy [35]. Young adults with ADPKD should be followed closely from diagnosis, with routine blood pressure monitoring ideally using ABPM, with careful assessment of associated extrarenal disease. Education for parents with ADPKD and for children with or at-risk for ADPKD is an important initial step in instilling the value of routine follow up for young adults with or at-risk for ADPKD.

ACKNOWLEDGEMENTS

We are grateful to Luke D.C. Miga for his expert help with figure redesign. A.C.M.O. acknowledges research funding from the Medical Research Council, Kidney Research UK, the National Institutes of Health and Care Research, the PKD Charity, and the PKD Foundation.

CONFLICT OF INTEREST STATEMENT

M.A.C. reports having received consultancy fees and serving on the paediatric research steering committee for Otsuka Pharmaceuticals, Inc.

A.C.M.O. reports having received consultancy fees from Galapagos, Janssen, Mironid, ONO, Palladio, and Sanofi-Genzyme, companies working in the field of ADPKD. All money is paid to his employing institution.

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