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Multimorbidity in autosomal dominant polycystic kidney disease

Wielochorobowość w autosomalnie dominującej wielotorbielowatości nerek

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Abstract

Background. *Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetically determined renal disorder. Due to the systemic nature of the disease, numerous extra-renal symptoms of ADPKD are observed. Therefore, multimorbidity, defined as living with at least 2 chronic illnesses, as well as polypharmacy, defined as using at least five medications daily, are common in ADPKD.* **Aim.** *The aim of our study was to describe the problems of multimorbidity and polypharmacy in ADPKD.* **Material and Methods.** *In a cross-sectional study, case records of adult ADPKD patients, in all phases of the disease, managed at our outpatient department, were reviewed. 164 patients were included:115 patients who did not require RRT (non-ESKD group), and 49 renal transplant recipients (Tx group).* **Results.** *At least 2 chronic diagnoses were noticed in 163 patients (99%). The median number of chronic diagnoses in the whole group was 5 (range 1-10, interquartile range (IQR) 3.0), and, there was a significant difference (p<0.01) in the number of chronic diagnoses between non-ESKD group (median 5, range 1-10, IQR 2.0) and Tx group (median 8, range 4-10, IQR 2.0). Polypharmacy was observed in 93 patients (57%) of the whole group, including 44 patients (38%) in the non-ESKD group, and 49 patients (100%) in the Tx group. The median number of medicines used in the whole group was 6 (range 0-19, IQR 7.5).* **Conclusions.** *Multimorbidity, as well as polypharmacy, are common in ADPKD patients. These facts have to be considered in the management of this group. Based on our results, we speculate that ADPKD may be considered a model of accelerated aging. (Gerontol Pol 2022; 30; 163-168) doi: 10.53139/GP.20223022*

Keywords: *autosomal dominant polycustic kidney disease; multimorbidity; polypharmacy.*

Streszczenie

Wstęp. *Autosomalnie dominująca wielotorbielowatość nerek (ADPKD) jest najczęstszą genetycznie uwarunkowaną chorobą nerek. Ze względu na układowy charakter choroby, istnieją liczne pozanerkowe manifestacje ADPKD. Dlatego wielochorobowość, definiowana jako współistnienie co najmniej 2 chorób przewlekłych, oraz wielolekowość, definiowana jako przyjmowanie co najmniej 5 leków na dobę, są częste w ADPKD.* **Cel.** *Celem pracy jest scharakteryzowanie ilościowe problemów wielochorobowości oraz wielolekowości w ADPKD.* **Materiał i metody.** *Badanie przekrojowe. Dane uzyskano z dokumentacji dorosłych osób z ADPKD we wszystkich fazach przewlekłej choroby nerek, pozostających pod opieką naszego ośrodka. Włączono 164 pacjentów: 115 niewymagających leczenia nerkozastępczego (grupa non-ESKD) i 49 biorców przeszczepienia nerki (grupa Tx).* **Wyniki.** *U 163 pacjentów (99%) stwierdzono co najmniej 2 choroby przewlekłe. Przeciętna liczba przewlekłych chorób w całej grupie wyniosła 5 (zakres 1-10, zakres międzykwartylowy (IQR) 3,0). Stwierdzono statystycznie istotną różnicę (p<0,01) w liczbie chorób przewlekłych między grupą non-ESKD (przeciętna 5, zakres 1-10, IQR 2,0) i grupą Tx (przeciętna 8, zakres 4-10, IQR 2,0). Wielolekowość stwierdzono u 93 pacjentów (57%) całej grupy, w tym u 44 pacjentów (38%) w grupie non-ESKD i 49 pacjentów (100%) w grupie Tx. W całej grupie przeciętna liczba przyjmowanych leków wyniosła 5 (zakres 0-19, IQR 7,5).* **Wnioski.** *Wielochorobowość i wielolekowość są powszechne w ADPKD. Fakty te trzeba uwzględniać w prowadzeniu tej grupy pacjentów. Nasze wyniki mogą sugerować, że ADPKD można traktować jako model przyspieszonego starzenia. (Gerontol Pol 2022; 30; 163-168) doi: 10.53139/GP.20223022*

Słowa kluczowe: *autosomalnie dominująca wielotorbielowatość nerek; wielochorobowość; wielolekowość.*

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetically determined renal disorder, with approximately 12.5 million of people involved worldwide. In a large proportion of patients, ADPKD leads to the end-stage kidney disease (ESKD) during adulthood, being responsible for even 10% of ESKD cases. In the vast majority of cases, ADPKD is caused by a mutation in PKD1 or PKD2 gene, encoding polycystin-1 (PC1) or polycystin-2 (PC2), respectively [1]. Due to the fact that polycystins are localized in numerous tissues [2], patients with ADPKD commonly have extrarenal symptoms. They include cysts in organs other than kidney (e.g. liver, pancreas, spleen), arterial hypertension, aneurysms, and many others [1]. With the progression of the chronic kidney disease (CKD), in ADPKD patients new health problems may occur, including a.o. cardiovascular [3] and neoplastic diseases [4]. Therefore, multimorbidity, defined as living with at least 2 chronic illnesses [5], is common in ADPKD. Multimorbidity leads to the worsening in health outcomes, increased complexity of the clinical management, as well as increased health care costs [5]. Complex multimorbidity (CMM) is another term associated with the problem of multimorbidity. It is defined as the number of body systems affected by the diseases. CMM is considered to be useful in identifying high-need individuals [6].

Aim

The primary aim of our study was to quantitatively describe the problem of multimorbidity, as well as CMM, in ADPKD patients.

Multimorbidity is frequently associated to polypharmacy, which means using of multiple medicines. According to the most common definition of polypharmacy, it may be recognized when a patient takes five or more medications daily. Polypharmacy leads to increased risk of adverse drug reactions, drug interactions, prescribing cascade, and higher costs of care [7]. Thus, the secondary aim of our study was to quantify the problem of polypharmacy in ADPKD.

Material and methods

In a cross-sectional study, case records of adult ADPKD patients, in all phases of the disease, managed at our outpatient department, were reviewed. Diagnosis of ADPKD was based on the ultrasonographic criteria [8]. Age, sex, serum creatinine, number of chronic diagnoses, encoded with International Classification of Diseases 10th Revision (ICD-10) codes, and number of medicines used at the moment of the last visit were recorded.

Statistical analysis was performed using Statistica 13.3 (StatSoft, Tulsa, OK, USA). Normality of data distribution was measured with the Shapiro-Wilk test. Nonparametric test were used in further analyses: Pearson's χ^2 test, Mann-Whitney U-test, Kruskal-Wallis one-way analysis of variance by ranks, and Spearman rank correlation. Results are presented as medians, range, and interquartile range (IQR). Results with $p < 0.05$ were considered statistically significant.

The study was conducted according to the principles of the Declaration of Helsinki. Due to the character of the study, the approval of the Ethics Committee, as well as written informed consent were redundant.

Results

164 patients fulfilled the inclusion criteria and were included into our study. Among them, 115 patients did not require RRT (non-ESKD group), and 49 patients were renal transplant recipients (Tx group). The characteristics of the study group are set out in table I.

Patients in the non-ESKD were younger and had better renal function compared to the Tx group.

At least 2 chronic diagnoses were noticed in 163 patients (99.4%). The median number of chronic diagnoses in the whole group was 5 (range 1-10, IQR 3.0), and, as could be expected, there was a significant difference ($p < 0.01$) in the number of chronic diagnoses between non-ESKD group (median 5, range 1-10, IQR 2.0) and Tx group (median 8, range 4-10, IQR 2.0). The median number of body systems affected by the diseases in the whole group was 5 (range 1-9, IQR 2.0), and, similarly, there was a significant difference ($p < 0.01$) in the num-

Table I. Characteristics of the study group

Characteristic	Whole group (n = 164)	Non-ESKD (n = 115)	Tx (n = 49)	p*
Men/women, n (%)	69/95 (42/58)	47/68 (41/59)	22/27 (45/55)	NS
Median age, years (range, IQR)	52 (20-88, 24)	43 (20-88, 22)	63 (40-81, 9)	p <0.01
Median serum creatinine, mg/dL (range, IQR)	1.18 (0.5-5.44, 0.84)	1.07 (0.5-5.44, 0.91)	1.39 (0.75-4.61, 0.60)	p <0.01

IQR: interquartile range; non-ESRD: patients without end-stage kidney disease; Tx: renal transplant recipients; NS; not statistically significant
*comparison between non-ESKD and Tx group

ber of body systems affected by the diseases between non-ESKD group (median 4, range 1-9, IQR 2.0) and Tx group (median 6, range 3-9, IQR 2.0). Significant differences were observed in number of chronic diagnoses as well as in the number of body systems involved between age groups in the whole group (both $p < 0.01$), and in the non-ESKD group (both $p < 0.01$), but not in the Tx group (table II).

Polypharmacy, defined as using at least five medications daily, was observed in 93 patients (57%) of the whole group, including 44 patients (38%) in the non-ESKD group, and 49 patients (100%) in the Tx group. The median number of medicines used in the whole group was 6 (range 0-19, IQR 7.5), and there was a significant difference ($p < 0.01$) in the number of medicines used between non-ESKD group (median 4, range 0-13, IQR 4.0) and Tx group (median 11, range 5-19, IQR 5.0). Additionally, there were significant differences ($p < 0.01$) in the number of medicines used between age groups (table III).

We did not found statistically significant correlation neither between age and number of chronic diagnoses, number of body systems involved by diseases, and number of medicines used nor between serum creatinine level and number of chronic diagnoses, number of body systems involved by diseases, and number of medicines used.

Discussion

Nephrologic patients belong to the most complex medical cases [9]. ADPKD seems to be even more complicated compared to other renal disorders due to the both renal, and extra-renal distribution of polycystins [2], leading to a systemic character of the disease [1]. Results of our study confirm the complexity of the ADPKD cases; almost all ADPKD patients have multimorbidity. Additionally, although correlations were not found, the number of chronic diseases and body systems involved is increased in the older age groups. This does not concern the oldest patients (9th decade of life), possibly due to the fact that persons with the largest number of diseases die before they reach that age.

According to the natural history of the disease, patients with ADPKD died when ESKD had developed, what may be illustrated by the case of the Polish king, Stefan Batory, who died in his 53rd year of life, and who is known as the first reported case of the disease [10]. The median age of ESKD in ADPKD patients is

Table II. Number of chronic diagnoses and body systems involved in age groups

Age group (years)	Whole group (n = 164)			Non-ESKD (n = 115)			Tx (n = 49)		
	N	Median number of chronic diagnoses (range, IQR)	Median number of body systems involved (range, IQR)	N	Median number of chronic diagnoses (range, IQR)	Median number of body systems involved (range, IQR)	N	Median number of chronic diagnoses (range, IQR)	Median number of body systems involved (range, IQR)
20-29	16	4 (2-5, 1)	3 (1-4, 2)	16	4 (2-5, 1)	3 (1-4, 2)	0	NA	NA
30-39	28	4 (2-7, 2)	4 (2-7, 2)	28	4 (2-7, 2)	4 (2-7, 2)	0	NA	NA
40-49	32	5 (1-7, 2)	5 (1-7, 2)	29	5 (1-7, 2)	4 (1-7, 1)	3	7 (6-7, 1)	6 (5-6, 1)
50-59	28	6 (3-9, 3)	6 (2-9, 2)	16	6 (3-9, 3)	5 (2-9, 2)	12	8 (4-9, 2)	6 (3-7, 2)
60-69	42	7 (4-10, 4)	5 (3-9, 1)	16	5 (4-7, 2)	5 (3-7, 1)	26	8 (5-10, 3)	6 (4-9, 2)
70-79	15	8 (4-10, 3)	6 (3-8, 2)	8	7 (4-10, 3)	7 (3-8, 3)	7	8 (6-10, 1)	6 (5-8, 2)
80-89	3	6 (6-8, 2)	5 (5-6, 1)	2	6 (NA)	5 (NA)	1	8 (NA)	6 (NA)

IQR: interquartile range; non-ESRD: patients without end-stage kidney disease; Tx: renal transplant recipients; NA: not applicable

Table III. Number of medicines used in age groups

Age group (years)	N	Number of medicines used		
		median	range	IQR
20-29	16	1	0-3	2
30-39	28	2	0-6	1
40-49	32	5	0-12	5
50-59	28	7	2-15	6
60-69	42	9	1-19	6
70-79	15	9	5-14	2
80-89	3	10	8-13	5

IQR: interquartile range

58 years-of-life when PKD1 gene is mutated, or 79 years-of-life when it is mutation of PKD2 gene what is responsible for the disease [11]. While in 85% of ADPKD cases it is the mutation in PKD1 what leads to the disease [1], the majority of ADPKD cases reach ESKD is their sixth decade of life. Since renal replacement therapy (RRT) became available in the second half of the XX century, the lifetime of ADPKD patients may be prolonged; however, new health problems usually occur during RRT, for example diabetes mellitus, which is tenfold more frequent after renal transplantation compared to pre-ESKD stages of the disease [12]. Similarly, frequency of cardiovascular [13] and neoplastic [14,15] complications is increased in this phase of CKD. Accordingly, our results show the increase in the number of health conditions in patients with ADPKD after the age of 50 years. Additionally, in line with our expectations, renal transplant recipients were older and had more diseases than the non-ESKD group. These facts are accompanied by increase in healthcare costs with the progression of CKD in ADPKD reported in the literature [16]. Therefore, a holistic approach is especially important in ADPKD patients, in which multimorbidity is taken into account. Preferably, a multispecialist team should be involved in the management of these patients, and multidirectional care should be provided to this group of patients. This has already been included in guidelines released by a Kidney Disease: Improving Global Outcomes (KDIGO) [1]. Additionally, polypharmacy is common in ADPKD, what was shown by our results. It leads to the risk of adverse events, and drug-drug interactions. This fact also need to be consulted in the care of ADPKD patients.

The control group was lacking in our study, and we, therefore, are not at liberty to compare the number of diseases between ADPKD and non-ADPKD cases. However, the number of chronic conditions observed in our group is higher compared to patients of a similar age reported in the study of Tonelli et al [17]. We realize these two studies are not fully comparable due to numerous reasons, however, we feel that it is highly probable that ADPKD patients are more complex than people without ADPKD. Economic analyses support our speculation; healthcare costs were shown to be increased in ADPKD compared to non-ADPKD controls [16].

Multimorbidity is a feature of aging [7]. Therefore, based on our results, we speculate that ADPKD may be considered a model of premature aging. In fact, premature aging is observed in the chronic kidney disease, and is mediated primarily by an endothelial dysfunction [18], which occurs early in the course of ADPKD [19]. Several clinical features seem to support our hypothesis. First, arterial hypertension, which is a common manifestation of ADPKD, begins approximately 15 years earlier compared to essential hypertension in the general population [20]. Second, the median age of rupture of intracranial aneurysms, which are another extrarenal manifestation of ADPKD, is approximately 10 years lower compared to the general population [21]. Third, as mentioned above, according to the natural history of the disease, the age in which the majority of patients died was the sixth decade of life. Additionally, the hazard ratio of all-cause mortality is increased in ADPKD patients compared to non-ADPKD controls [22]. Moreover, similar mechanisms were reported to be involved both in aging as well as in the progression of ADPKD, e.g. m-TOR pathway [23,24]. Consequently, similar proceedings were proposed to slow both the aging and the progression of ADPKD, including metformin [25,26], PPARγ agonists [27,28], caloric restriction [29,30], intermittent fasting [29,31], time restricted feeding [29,32], and ketogenic diet [29,33]. According to Dritsoula et al. [34], CKD is not associated with the increase in the "DNA methylation age;" however, the authors of that study did not specify, whether ADPKD patients were included into the study group [34]. Due to the fact that ADPKD differs in many aspects from other conditions leading to CKD, we feel that the question whether "DNA methylation age" is not increased compared to the chronological age in ADPKD should be examined. When accelerated epigenetic aging in ADPKD is proven, methods considered efficient in reversal of it [35] should be tested in ADPKD patients.

Limitations of our study should be acknowledged. First, the data were obtained from case records, and some information could be incomplete. Second, mutations leading to ADPKD have not been identified in our group; therefore, we were not able to seek for an association between the mutation type and multimorbidity or polypharmacy. Third, due to the methodological differences, our study may be not comparable to other studies. However, we feel that these limitations does not impact our results significantly.

Conclusions

Multimorbidity, as well as polypharmacy, are common in ADPKD patients. These facts have to be considered in the management of this group. Based on our results, we speculate that ADPKD may be considered a model of accelerated aging.

Conflict of interest
none

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