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Prevalence of Cognitive Impairment in Peritoneal Dialysis Patients and Associated Factors

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Keywords
Cognitive impairment · Chronic kidney disease · Peritoneal dialysis · Addenbrooke's Cognitive Examination III test · Screening test

Abstract
Background: Cognitive impairment (CI) in patients with chronic kidney disease, including those treated with renal replacement therapy, is a growing problem worldwide. ***Objectives:*** The study aimed to assess the prevalence of CI and associated factors in patients undergoing peritoneal dialysis (PD). ***Methods:*** In this cross-sectional study, 18 consecutive patients with PD therapy and 15 controls were evaluated for CI using the Addenbrooke's Cognitive Examination III (ACE III) test. ***Results:*** The prevalence of CI was 33% in patients and 27% in the control group and was not statistically significant. A higher prevalence of CI was found in subjects aged ≥65 years old than in those <65 years old ($p = 0.02$), but only in the control group. The prevalence of CI in PD patients over and under 65 years of age did not differ statistically significantly ($p = 0.12$). Memory and verbal fluency were the most affected cognitive domain in PD patients with CI ($p = 0.00$, $p = 0.04$, respectively). There was a significant correlation between higher educated PD patients and the ACE III test results. The duration of dialysis did not affect the results of the cognitive screening test. ***Conclusions:*** CI is a growing problem in the course of chronic kidney disease and dialysis therapy. It seems that cognitive problems may occur in patients undergoing PD at a younger age than in the general population with particularly affected memory and verbal fluency. Higher educated patients score better on the cognitive screening test.

Introduction

Cognitive impairment (CI) may be defined as a clinical syndrome characterized by a decline in at least two out of several domains of cognitive function [1], like attention/working memory, new verbal learning, recall, expressive language, visual construction, executive functions, abstract reasoning [2]. This ranges from mild deficits, which are not clinically detectable, to dementia [3]. CI is a growing problem worldwide. The prevalence increases

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with age and, in addition to age, it might have a variety of possible causes, education level, depression, cerebrovascular disease, or metabolic derangements [4]. Chronic kidney disease (CKD) is an independent risk factor for cognitive decline [5–7], and the prevalence in patients with end-stage renal disease is estimated at 50–80% [8, 9]. CI significantly increases the risk of hospitalization, mortality, and a poorer quality of life [10]. Problems with cognitive functioning were also observed in patients undergoing renal replacement therapy (RRT), both peritoneal dialysis (PD) and hemodialysis, also in non-elderly patients [11]. It seems that the CI of patients on RRT may be underdiagnosed. Moreover, little is known about the prevalence of CI in patients undergoing PD [12]. Patients on PD with cognitive problems might not be able to continue this form of dialysis. Unfortunately, screening for cognitive decline is not yet a routine practice, and there is no standard neuropsychological test. For this reason, the results of studies are inconclusive. Based on a different battery of screening tests, it was reported that the prevalence of CI in patients on PD ranges from 22.3 to 74.5% [13–16]. The goal of the study was to determine the frequency of CI in patients undergoing PD and associated factors and compared them to the control group.

Materials and Methods

In this cross-sectional study, 18 consecutive patients with PD and 15 controls, who consented to participate in the study, were evaluated for cognitive function using the Addenbrooke's Cognitive Examination III (ACE III) test. Four patients declined to participate in the study. We included patients on PD, clinically stable without infectious disease in the last 6 weeks, decompensated heart or liver failure, psychiatric or neurodegenerative disorders, and delirium. Moreover, patients who did not speak Polish or could not complete the questionnaire independently, or have significant visual/hearing disabilities were also excluded. Furthermore, demographic data and medical history (primary renal disease, duration of dialysis) were obtained from hospital clinic records. The control group was recruited from healthy volunteers (employees of the Department of Neurology) and patients of the Department of Neurology, after excluding diseases of the central nervous system and CKD. The control group was matched by age and sex to a random sample of patients with PD.

Cognitive Function Evaluation

The A version of the ACE III test was used to evaluate cognitive function including, attention, memory, verbal fluency, language, and visuospatial abilities with a score ranging from zero to 100 points. All PD patients and controls were assessed in a separate room, in silence, and at about the same time by one of two researchers. According to Takenoshita et al. [17], a cut-off point of ≤88% (sensitivity 0.77, specificity 0.92) was established for CI. We decided to use the ACE III test for several reasons, including (1) the test can be performed by both physicians and other healthcare professionals, (2) it has been verified by five standard tests: Wechsler Adult Intelligence Scale-Digit Scale (WAIS-DS), Rey Auditory Verbal Learning (RAVLT), Sydney Language Battery (SydBAT), Rey-Osterrieth Complex Figure Test (ROCFT), and Frontotemporal Dementia Functional Rating Scale (FTDFRS) [15], (3) has good sensitivity and specificity for CI detection, (4) has a Polish version and is available free of charge.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics 26.0. The Pearson correlation analysis was used to verify the statistically significant dependence between the analyzed variables. Comparison between various subgroups was carried out with use of the Student's t test and χ^2 test. Statistical significance was taken as $p < 0.05$.

Results

Eighteen patients and 15 controls' age and sex matched were included in the study. The demographic and clinical characteristics of the subjects are summarized in Tables 1, 2. The mean age was 50 ± 19 years and 49 ± 20 years in patients and controls, respectively. Most patients and controls were women under the age of 65 (shown in Table 1). The mean PD duration was 47.6 ± 37.9 months. Education level and gender were similar in PD patients and the control group (shown in Table 2). The mean ACE III score in PD patients and controls was 89.3 ± 10.3 and 93.6 ± 8.2, respectively ($p = 0.2$, shown in Table 3). In PD patients, the prevalence of CI was 33%, whereas in the control group it was 27% and did not differ significantly ($p = 0.6$, shown in Table 3). A higher prevalence of CI was found in controls in those ≥65 years old ($n = 3$), than in those <65 years old ($n = 1$) ($p = 0.02$, shown in Table 4). Interestingly, the prevalence of CI in PD patients over and under 65 years of age did not differ statistically significantly ($p = 0.12$, shown in Table 4). There was a significant trend for PD patients with CI to score lower in the domains of memory ($p = 0.00$) and verbal fluency ($p = 0.04$, shown in Table 5). Moreover, the correlation coefficient between the total ACE III test scores and the domains of memory, verbal fluency, language, and the years of education of patients and controls revealed a significant relationship between a higher educated person and the test results, but only in PD patients (shown in Table 6; Fig. 1, 2). In controls, the values of the correlation coefficient do not exceed 0.6 (shown in Table 6; Fig. 1). There was no correlation between the duration of dialysis and the results of the ACE III test (shown in Table 6).

Table 1. Demographic characteristics of the study group

	PD patients			Controls			*p* value*	*p* value**	*p* value***
	all (*n* = 18)*	<65 years (*n* = 13)**	≥65 years (*n* = 5)***	all (*n* = 15)*	<65 years (*n* = 10)**	≥65 years (*n* = 5)***			
Age, mean±SD (range), years	50±19 (21–75)	42±16 (21–64)	72±3 (66–75)	49±20 (20–80)	39±14 (20–64)	72±5 (66–80)	0.9	0.6	0.8
Female, *n* (%)	13 (72)	8 (44)	5 (28)	12 (80)	8 (53)	4 (27)	–	–	–
Years of education, mean±SD (range)	14.5±3.4 (7–20)	15.5±3 (8–20)	12±3 (7–16)	14.1±2.7 (10–18)	15±2.5 (11–18)	12.4±2.3 (10–16)	0.7	0.7	0.8

p: two-tailed significance level in Student's *t* test.

Table 2. Characteristics of the patient group

Causes of renal failure, *n* (%)	PD patients		
	all (*n* = 18)	no cognitive impairment (*n* = 12)	cognitive impairment (*n* = 6)
Tubulointerstitial nephritis	3 (16.7)	2 (16.7)	1 (16.7)
Polycystic kidney disease	2 (11.1)	1 (8.3)	1 (16.7)
Unknown cause	4 (22.1)	3 (25)	1 (16.7)
Hemolytic uremic syndrome	1 (5.6)	1 (8.3)	0
Chronic glomerulonephritis	5 (27.7)	3 (25)	2 (33.3)
Congenital abnormality	1 (5.6)	1 (8.3)	0
Systemic lupus erythematosus	1 (5.6)	0	1 (16.7)
Diabetic nephropathy	1 (5.6)	1 (8.3)	0
Dialysis duration, months, mean±SD (range)	47.6±37.9 (1–110)	37.8±36.5 (1–110)	65.2±37.3 (16–109)

Discussion

In the present study, we found that 33% of PD patients and 27% of controls were cognitively impaired, which is in line with a recently published meta-analysis [18]. Shea et al. [18] reported a pool prevalence of CI among PD patients at 28.7% with risk factors such as older age, female gender, and lower education. On the other hand, Neumann et al. [19] indicated that the prevalence of CI among PD patients was much lower at 15%. They assessed cognitive functions in dialysis patients using 3 tests, i.e., cognitive function reported by the patient, and 2 tests assessing selective executive functioning and attention. In our study, patients and controls were evaluated in 5 cognitive domains, i.e., attention, memory, verbal fluency, language, and visuospatial function, which may lead to increased detection of CI. Nevertheless, other studies found that over 50% of PD patients had cognitive problems and it was associated with older age, lower education, and lower sodium and creatinine levels [13, 20]. Furthermore, in our study in the control group, CI was more common in subjects ≥65 years old, which is in line with global trends of increasing CI with age [4]. On the other hand, we showed that cognitive decline in PD patients may occur earlier (<65 years) than in the general population. One of the explanations might be multimorbidity among PD patients or continuous exposure to uremic toxins; however, the underlying mechanism is likely to be more complex. Therefore, PD patients should be routinely assessed in terms of cognitive deterioration. We also showed a strong effect of higher education level on total ACE III score and the domains of memory, verbal fluency, and language, but only for the PD patients. This suggests that better education plays a protective role against cognitive decline in PD patients. Higher educated PD patients may have a large enough cognitive reserve to prevent early deterioration in cognitive functions and are better able to perform cognitive tests. Cognitive reserve is a theoretical term introduced by Stern [21] to explain individual variability in coping with brain damage. Individuals with high cognitive reserve retain the ability to deal with brain changes longer and more efficiently than

Table 3. The results of ACE III test

Variable	PD patients			Controls			*p* value*		
	all (*n* = 18)	CI (*n* = 6)	NCI (*n* = 12)	all (*n* = 15)	CI (*n* = 4)	NCI (*n* = 11)	*p* (all)	*p* (CI)	*p* (NCI)
ACE III test									
Total score, mean ± SD (min-max)	89.3±10.3 (61–99)	78.5±11.6 (61–88)	94.8±2.7 (89–99)	93.6±8.2 (75–100)	81.5±4.5 (75–85)	98±2.8 (92, 100)	0.2	0.6	0.01
Attention, mean±SD (min, max)	93.2±9 (72–100)	91.5±10.4 (72–100)	94±8.7 (89–99)	95.9±5.3 (89–100)	93±5.2 (89–100)	97±5.1 (89, 100)	0.3	0.8	0.3
Memory, mean±SD (min, max)	83.5±17.9 (46–100)	60.8±8.9 (46–73)	94.8±6.3 (81–100)	89.6±14.6 (58–100)	69±13 (58–88)	97±4 (88, 100)	0.3	0.3	0.3
Fluency, mean±SD (min, max)	79.9±19.6 (28–100)	62±24.5 (28–86)	88.9±7.6 (79–100)	87.6±16.8 (57–100)	67.8±13.8 (57–86)	94.8±11.2 (64, 100)	0.2	0.6	0.16
Language, mean±SD (min, max)	95.9±7.3 (77–100)	91±11 (77–100)	98.3±2.7 (92–100)	96.1±6.8 (77–100)	88.5±9.8 (77–100)	98.9±1.9 (96, 100)	0.9	0.7	0.5
Visuospatial, mean±SD (min, max)	92±13.2 (56–100)	86.5±18 (56–100)	94.8±9.9 (75–100)	96.7±9.7 (62.5–100)	89.1±18 (62.5–100)	99.5±1.8 (94, 100)	0.2	0.8	0.14

CI, cognitive impairment; NCI, no cognitive impairment. *Two-tailed significance level in Student's *t* test.

Table 4. Prevalence of CI in PD patients and controls depending on age

Cognitive impairment					
PD patients (*n* = 6)			controls (*n* = 4)		
<65 years (*n* = 3)	≥65 years (*n* = 3)	*p* value	<65 years (*n* = 1)	≥65 years (*n* = 3)	*p* value
23%	60%	0.14	10%	60%	0.02

p: asymptotic significance level in two-sided χ^2 test.

individuals with lower cognitive reserve [21]. Few studies showed that patients undergoing PD therapy have a higher prevalence of brain abnormalities on magnetic resonance imaging, such as more severe white matter changes or brain atrophy as compared to the general population [22, 23]. The cognitive reserve theory and the higher prevalence of brain pathology in PD patients may partially explain the results of our research. In other words, higher educated PD patients, even with the presence of anatomic changes in the brain, may have better cognitive performance. Moreover, we did not find any correlation between the duration of dialysis and the results of the ACE III test, which is in accordance with previous reports [18]. Although the difference in dialysis duration between CI and non-CI patients seems large (Table 2), the correlation between dialysis duration and ACE III test score is close to zero (Table 6). This is probably due to the small size of the group. Finally, we found a significant trend for PD patients with CI to score lower in the domains of memory and verbal fluency. The pattern of cognitive disorder in our PD patients resembles both Alzheimer's disease with prominent impairment of

Table 5. The results of ACE III test in cognitive impairment (CI) and no cognitive impairment (NCI) PD patients

Variable	PD patients		*p* value*
	CI (*n* = 6)	NCI (*n* = 12)	
ACE III test			
Total score, mean±SD (min, max)	78.5±11.6 (61–88)	94.8±2.7 (89–99)	0.018
Attention, mean±SD (min, max)	91.5±10.4 (72–100)	94±8.7 (72–100)	0.626
Memory, mean±SD (min, max)	60.8±8.9 (46–73)	94.8±6.3 (81–100)	0.00
Fluency, mean±SD (min, max)	62±24.5 (28–86)	88.9±7.6 (79–100)	0.042
Language, mean±SD (min, max)	91±11 (77–100)	98.3±2.7 (92–100)	0.165
Visuospatial, mean±SD (min, max)	86.5±18 (56–100)	94.8±9.9 (75–100)	0.327

*Two-tailed significance level in Student's *t* test.

Table 6. Correlation coefficient between years of education and dialysis duration and the results of the ACE III test for PD patients and controls

			ACE III total score (%)	Attention (%)	Memory (%)	Verbal fluency (%)	Language (%)	Visuospatial (%)
PD patients (*n* = 18)	Years of education	Pearson correlation	0.78**	0.19	0.63**	0.84	0.73**	0.56*
		Significance	0.00	0.45	0.005	0.00	0.00	0.02
	Dialysis duration (months)	Pearson correlation	−0.19	−0.08	−0.33	−0.05	−0.08	0.2
		Significance	0.46	0.76	0.18	0.84	0.75	0.93
Controls (*n* = 15)	Years of education	Pearson correlation	0.53	0.41	0.52*	0.44	0.52*	0.31
		Significance	0.04	0.13	0.046	0.1	0.049	0.26

**Two-tailed significance level, $p \leq 0.01$. *Two-tailed significance level, $p \leq 0.05$.

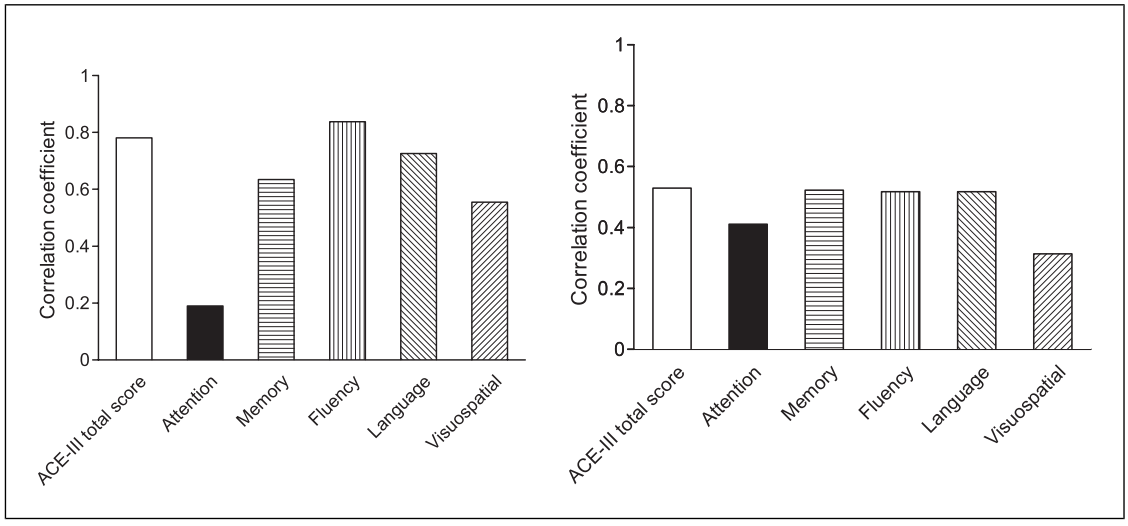

Fig. 1. Correlation coefficient between PD patients and years of education and the results of the ACE III test (left panel) and correlation coefficient for control between years of education and the results of the ACE III test (right panel).

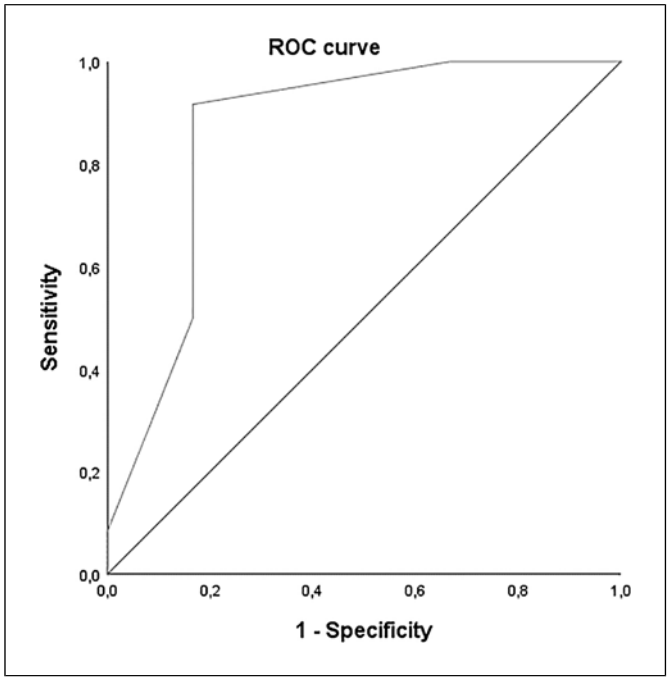

Fig. 2. ROC curve for classifier of PD patients representing the norm based on years of education.

memory and vascular dementia with impaired verbal fluency. It seems that the pathogenesis of CI may be more complex and mixed, and the different pathologies may underlie CI in PD patients.

There are some limitations associated with this study. A small number of PD patients and controls were included in the study, which was probably the reason for the large scatter in the data. Therefore, the results of our study should be treated with caution. More research is needed in this area. In addition, due to the small number of subjects, we could not conduct a separate analysis to determine the prevalence of mild CI and dementia. Moreover, vascular risk factors were not included in the statistical analysis.

CI in CKD, including patients undergoing RRT, is an increasing challenge for the healthcare system. It has an enormous impact on daily activity, quality of life, adherence to medical recommendations, and the choice of the method of RRT. On the other hand, there is growing awareness that CI is common in patients with CKD [24]. Therefore, screening for cognitive decline should be part of the routine follow-up visit.

Statement of Ethics

The local Ethics Committee at the Medical University of Warsaw, Warsaw, Poland, approved the study protocol, approval number KB/81/2022. Written informed consent was obtained from all participating subjects.

Conflict of Interest Statement

Authors report no conflict of interest.

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Author Contributions

A.G. and J.M. contributed to the conception and study design and drafted the manuscript and revised its final version; A.G. and P.O. contributed to subject assessment and data acquisition; E.W. and T.G. contributed to subject assessment; N.Z. contributed to statistical analysis and drafting of tables and figures. All authors gave final approval of the submitted manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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