

Mild cognitive impairment in maintenance hemodialysis patients: a cross-sectional survey and cohort study

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Introduction: Few studies focused on mild cognitive impairment (MCI) in maintenance hemodialysis (MHD) patients. This study was conducted to survey the prevalence, the potent risk factors of MCI in MHD patients, and further observe the progress of MCI in a period of 6 months.

Methodology: Mini-Mental State Examination, and Montreal Cognitive Assessment were used to assess cognitive condition. MHD patients were enrolled from The First Affiliated Hospital of Nanjing Medical University, who had a stable hemodialysis history for more than 3 months.

Results: Sixty-four MHD patients and 54 general subjects were finally included. The average age of both groups was more than 60 years. The prevalence of MCI in the MHD group was significantly higher than that in general population (60.9% vs 29.6%, $P < 0.05$). Spearman correlation analysis indicated that MCI was related to age, comorbidities, education years, uric acid, serum albumin, and blood pressure. The prevalence and severity of MCI in the MHD group remained unchanged during the 6 months (prevalence: 59.5%–66.6%, MoCA scores: 22.9–22.5).

Conclusion: MHD patients sustain a fairly high prevalence of MCI. Multiple risk factors influence the incidence and progression of MCI in MHD patients. More attention should be paid to this special population.

Keywords: dementia, end stage renal disease, Montreal Cognitive Assessment, Mini-Mental State Examination

Introduction

Mild cognitive impairment (MCI), an intermediate state from normal aging to dementia,¹ has gradually aroused global health professionals' interests.² McDaniel advocated for the first time in 1971 that cognitive dysfunction may correlate with renal failure.³ Then, Hagberg further demonstrated in 1974 that end-stage renal disease (ESRD) and hemodialysis (HD) could be associated with cognitive impairment.⁴ Afterward, Thorleif and Murray proposed that chronic kidney disease (CKD) patients might be more vulnerable to MCI.^{5,6} However, studies focusing on maintenance hemodialysis (MHD) with MCI are just few available.

Thus, this study was designed to observe the prevalence, associated risk factors, and progression of MCI in this specific population.

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Methodology

Participants

A total of 64 MHD and 54 general patients in the First Affiliated Hospital of Nanjing Medical University between October 2014 and October 2015 were eventually included (Figure 1). All participants signed informed consents. Ethics committee of the First Affiliated Hospital of Nanjing Medical University approved this study. Inclusion criteria are as follows: MHD – stable and regular HD (three times per week and 4 hours each time) that lasted for more than 3 months, general participants – subjects without CKD and acute kidney injury. Exclusion criteria are as follows: serious neurodegenerative disease and dementia.

MCI diagnostic criteria

The diagnostic criteria for MCI referenced the 2010 China guidelines⁷ and the 2014 *JAMA* advocacy.⁸ First, MCI was diagnosed through clinical dementia rating and chief complaints. Second, basic activities of daily living (ADL) were reserved, based on the Barthel index scale questionnaire. Third, patients should be free of dementia. These abovementioned judgments and diagnosis were made by a senior neurologist.

Covariates and measurements

The related clinical characteristics and laboratory parameters were determined, including age, gender, education years,

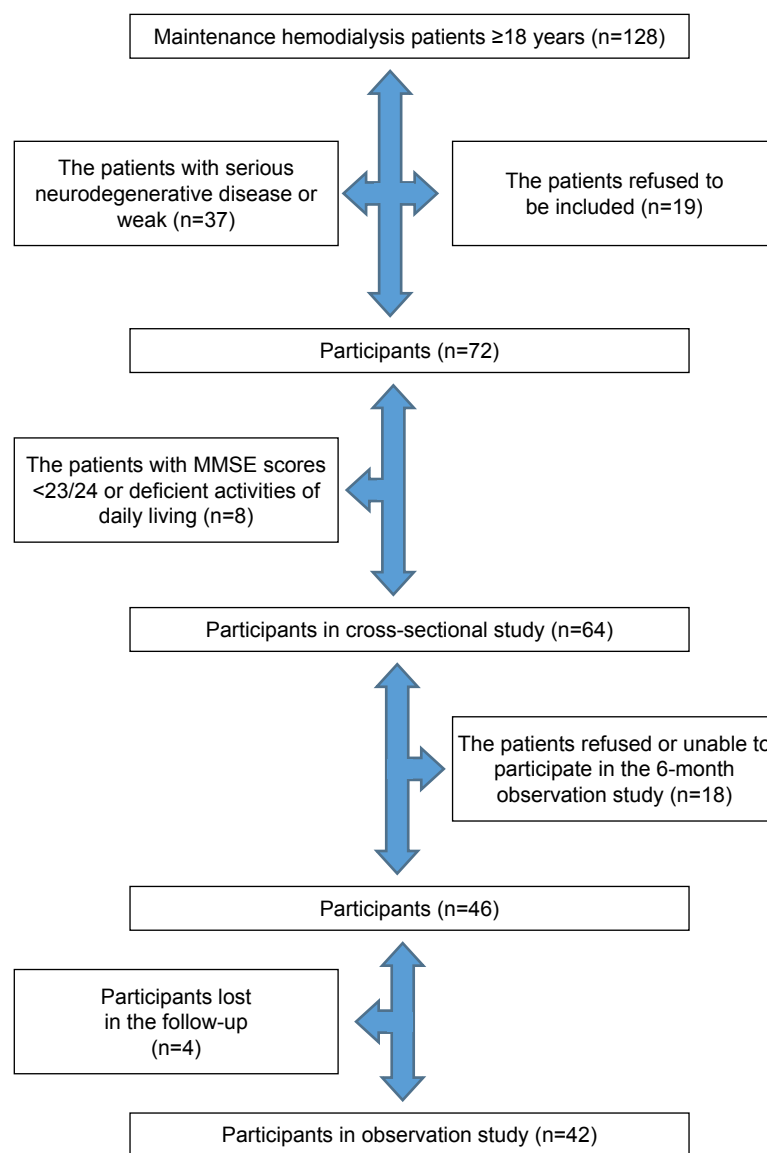


Figure 1 Flow chart of the subject inclusion.

Abbreviation: MMSE, Mini-Mental State Examination.

comorbidities, dialysis age, body mass index (BMI), serum creatinine, serum urea nitrogen, uric acid, parathyroid hormone (PTH), albumin, hemoglobin, ferritin, urea reduction ratio (URR), and blood pressure.

Survey and cohort study

Questionnaires were carried out by the end of each HD treatment. The same questionnaires were repeated again 6 months later.

Statistical analyses

All the continuous variables were presented as mean±SD. Spearman correlation test was applied to ascertain the risk factors of MCI. The McNemar test and Wilcoxon test were measured to understand the progress of MCI. * $P<0.05$ and ** $P<0.01$ indicated statistical significance. All analyses were conducted using SPSS version 20 (IBM Corporation, Armonk, NY, USA).

Results

Basic characteristics

Following the inclusion and exclusion criteria, 64 MHD and 54 general patients were finally included. The mean age of both groups was more than 60 years. The dialysis age in the MHD group was 2.9 ± 2.2 years, with URR $69.3\%\pm 5.6\%$. Both the groups were matched for basic parameters such as age, gender, education years, and complications. The prevalence of lacunar infarction and hypertension in the MHD group was higher than that of the general group but did not reach statistical significance. Additionally, due to renal insufficiency, the concentration of most of the laboratory indexes in the MHD group was much higher than that of the general group, except serum calcium and albumin (Table 1).

Prevalence of MCI in MHD patients

The prevalence of MCI in the MHD group was much higher than that in the general group (60.9% vs 29.6%, on the basis of Montreal Cognitive Assessment [MoCA]) with OR 3.71. Mini-Mental State Examination questionnaire indicated that the impaired cognitive functions were the attention and recall parts. MoCA scale showed that MHD patients experienced more serious cognitive deficits, including visuospatial executive function, attention, language, abstraction, and delayed memory (Figure 2).

MCI risk factors

Spearman correlation test indicated that age, comorbidities, education years, uric acid, serum albumin, and blood pressure

Table 1 Basic characteristics of the subjects

Characteristics	MHD group (N=64)	General participants (N=54)
Age (years)	61 (17)	65 (18)
Gender (male)	44 (68.8%)	35 (64.8%)
Education (years)	11 (4)	12 (4)
Comorbidities		
Hypertension	45 (70.3%)	32 (59.3%)
Diabetes	16 (25.0%)	13 (24.1%)
Lacunar infarction	27 (42.2%)	21 (38.9%)
Lab parameters		
Scr ($\mu\text{mol/L}$)	863.33 (254.61)	73.3 (19.57)***
BUN (mmol/L)	26.6 (6.3)	5.5 (2.4)***
Uric acid ($\mu\text{mol/L}$)	397.2 (77.0)	308.8 (116.9)***
Potassium (mmol/L)	5.0 (0.7)	4.0 (0.4)***
Calcium (mmol/L)	2.27 (0.17)	2.25 (0.12)
Phosphonium (mmol/L)	1.75 (0.54)	1.06 (0.21)***
Albumin (g/L)	36.5 (4.8)	37.5 (5.5)
Hemoglobin (g/L)	96.2 (14.9)	123.4 (20.6)***
BMI (kg/m^2)	21.7 (4.2)	23.9 (4.0)**
SBP (mmHg)	144 (20)	128 (13)***
DBP (mmHg)	81 (15)	71 (12)**
PTH (ng/mL)	328.1 (293.3)	NR
Ferroprotein (g/L)	290.2 (372.3)	NR
Dialysis ages	2.9 (2.2)	NR
Urea reduction ratio	69.3% (5.6%)	NR

Notes: Cell values are represented as mean (SD) and n (%). ** $P<0.01$ and *** $P<0.001$, compared with the MHD group.

Abbreviations: MHD, maintenance hemodialysis; Scr, serum creatinine; BUN, blood urea nitrogen; BMI, body mass index; PTH, parathyroid hormone; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported.

were related to MCI in MHD patients, except gender, hemoglobin, ferritin, BMI, PTH, and dialysis age (Table 2).

Development of MCI with MHD during 6 months

Forty-two MHD patients consented in a further cohort observation study. The dialysis pattern and volume remained the same. During 6 months, the prevalence and severity of MCI have almost unchanged (prevalence: 59.5%–66.6%, MoCA scores: 22.9–22.5) (Table 3 and Figure 3).

Discussion

MCI, a syndrome with ADL retained and cognitive domain recession, captures increasing attractions.^{9–11} Immense amounts of studies have proved that MCI is the initial stage of dementia. Early diagnosis and intervention of MCI have been recognized as an essential step to prevent the onset of dementia.¹²

Among the previous studies, several researchers proposed that CKD patients are susceptible population of MCI. Along with the decline of renal function, cognitive functions are getting worse.¹³ Dialysis means kidney function paces

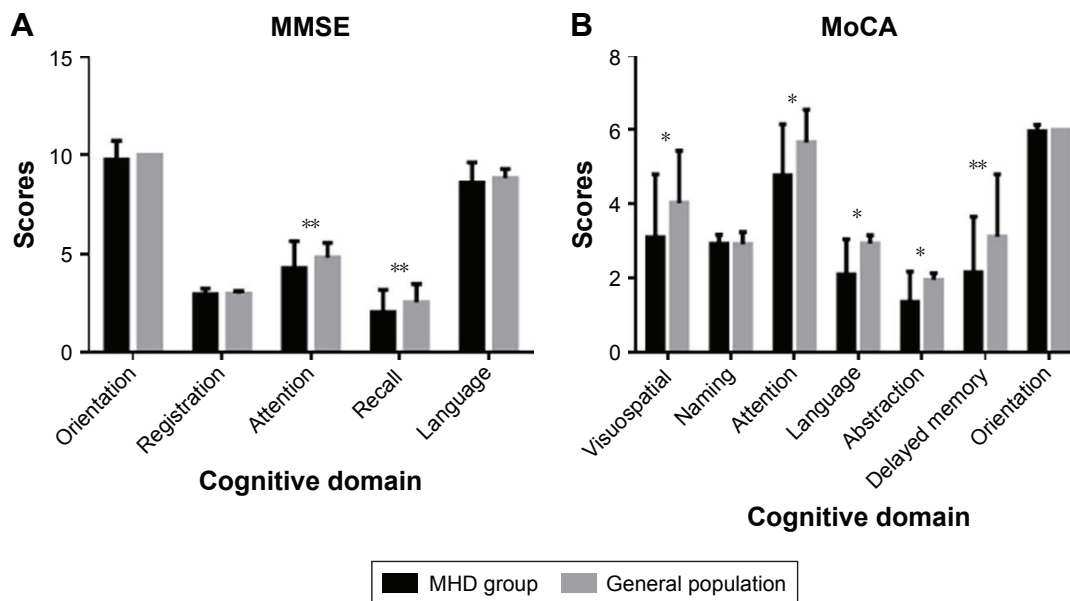


Figure 2 Detailed manifestation of MCI between the MHD group and general population. **Notes:** (A and B) Vertical coordinates were cognitive domain scores. Horizontal axes were name of cognitive domains. * $P < 0.05$ and ** $P < 0.01$ indicated statistical significance. **Abbreviations:** MCI, mild cognitive impairment; MHD, maintenance hemodialysis; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

to the end. For MHD patient, sound cognitive function is of great importance,¹⁴ as they have to draw more attention than general patients, to understand, remember, and follow the complicated medical treatments, such as diet control, fluid intake ration, medication therapy, and so on. Once the self-management ability of MHD patients was deprived or impaired, the incidence of tumble and mortality would rapidly increase.¹⁵ However, little if any studies have attached importance to MCI in the MHD population by far,¹⁶ especially in China, which will soon be the biggest dialysis country. What are the morbidity rate and the risk factors of MCI in

MHD patients? How to effectively delay the MCI process for dialysis patients?

Our results showed that the prevalence of MCI in MHD patients (60.9%) was twice as many as general population (29.5%), which was similar to the previous reports.¹⁷ Therefore, a fairly high prevalence of MCI is indeed ubiquitous in the MHD patients. So, what are the reasons that bring about such a high prevalence? Our results revealed that apart from the traditional causes, such as aging and education years, comorbidities, uric acid, serum albumin, and blood pressure were also related to the occurrence of MCI in MHD patients. As shown in our results, previous studies also found that for dialysis population, other than common risk factors, uremic toxin accumulation,¹⁸ vascular endothelial injury, hormone deficiency, malnutrition, blood exposure, anemia, and dyslipidemia were closely related to cognition dysfunction.¹⁹ Uric acid and blood pressure were independent risk factors with MCI.²⁰ Thereout, MHD patients have more exposures to susceptibility factors of MCI. To efficiently prevent the

Table 2 A list of risk factors with MCI

Variables	R
Age (years)	-0.597***
Gender	-0.162
Education years	0.436***
Comorbidities	-0.456***
Uric acid	0.293*
Albumin	0.310*
PTH	0.182
Hemoglobin	0.113
Ferroprotein	0.046
BMI	-0.184
SBP	0.280*
DBP	0.293*
Dialysis ages	-0.075

Notes: * $P < 0.05$, *** $P < 0.001$. R, relationship coefficient. **Abbreviations:** MCI, mild cognitive impairment; PTH, parathyroid hormone; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Prevalence and severity of MCI in MHD patients after 6 months

	Baseline	6 months later
MCI prevalence	25 (59.5%)	28 (66.6%)
MoCA scores	22.9 (5.4)	22.5 (5.9)

Notes: Cell values represent mean (SD) and n (%). The cutoff value of MoCA was 26. **Abbreviations:** MCI, mild cognitive impairment; MHD, maintenance hemodialysis; MoCA, Montreal Cognitive Assessment.

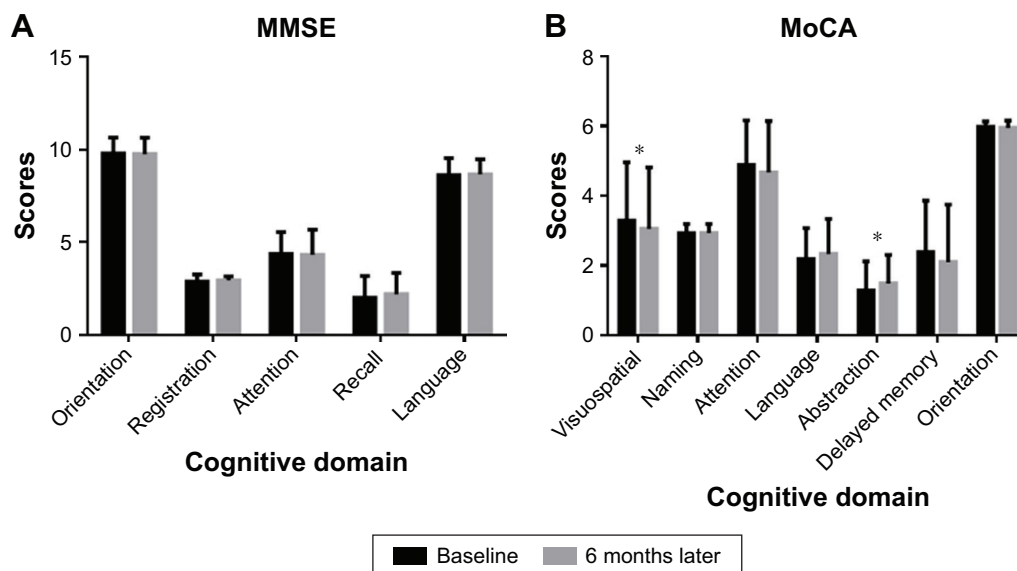


Figure 3 Progress of MCI with MHD during 6 months.

Notes: (A and B) Vertical coordinates were cognitive domain scores. Horizontal axes were name of cognitive domains. * $P < 0.05$ indicated statistical significance. **Abbreviations:** MCI, mild cognitive impairment; MHD, maintenance hemodialysis; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

onset of MCI, more attention should be paid and various measures should be taken.

The first and foremost way is to screen cerebrovascular event, which is a familiar and vital reason for cognition dysfunction.^{21,22} The onset of MCI could always be along with the occurrence of lacunar strokes. The phosphodiesterase III inhibitor cilostazol, which is often used in the prevention of stroke²³ and peripheral artery disease,²⁴ may delay cognitive decline.²⁵ There is one more method that should be touched on; once they are diagnosed as MCI, cognitive enhancers, including cholinesterase inhibitors²⁶ and memantine,²⁷ are recommended to treat the disease. Last but not the least, crucial measure should focus on the dialysis duration, dialysis adequacy, and dialysis pattern. A longer HD duration may correlate with a lower dementia risk, based on an analysis of over 200 thousand HD patients in Japan.²⁸ Frequent HD schedules might associate with reduced levels of dialysis-induced cardiac injury.²⁹ Dialysis adequacy is calculated based on small molecular uremic toxin (urea). But comorbidities such as cardiovascular disease and neuropathy are caused mainly by middle molecular and protein-bound uremic toxin. So, the current dialysis techniques cannot improve patient prognosis further,³⁰ which had also been elucidated in the HEMO study. Daily HD or nocturnal dialysis may have no benefit, compared with ordinal HD.³¹

Conclusion

MHD patients are prone to MCI, and great concerns should be focused on this specific population. Susceptible factors in

MHD patients were more complicated than those in general population. A longer prospective cohort study with more subjects might provide more credible information.³²

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Author contributions

WHZ conceived and designed the study. JQW guided and advanced the study. SYL, XHP, XLH, and HCY performed the experiments. XHP, SYL, ZZY, and BZ analyzed the experimental data. XHP, SYL, and NPM wrote the manuscript. XHP and WHZ reviewed and edited the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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