

# Author's Accepted Manuscript

Neurocognitive disorders in chronic kidney disease (CKD): A case report and literature review

Hiroshi Tateishi, Joji Maruo, Yoshinori Haraguchi, Tomoyuki Noguchi, Yoshito Mizoguchi, Takahiro A Kato, Toshiro Kawashima, Akira Monji



PII: S0033-3182(15)00120-6  
DOI: <http://dx.doi.org/10.1016/j.psym.2015.07.007>  
Reference: PSYM564

To appear in: *Psychosomatics*

Cite this article as: Hiroshi Tateishi, Joji Maruo, Yoshinori Haraguchi, Tomoyuki Noguchi, Yoshito Mizoguchi, Takahiro A Kato, Toshiro Kawashima, Akira Monji, Neurocognitive disorders in chronic kidney disease (CKD): A case report and literature review, *Psychosomatics*, <http://dx.doi.org/10.1016/j.psym.2015.07.007>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Neurocognitive disorders in chronic kidney disease (CKD): a case report and literature review**

Hiroshi Tateishi<sup>a</sup>, Joji Maruo<sup>a</sup>, Yoshinori Haraguchi<sup>a</sup>, Tomoyuki Noguchi<sup>b</sup>, Yoshito Mizoguchi<sup>a</sup>, Takahiro A Kato<sup>c</sup>, Toshiro Kawashima<sup>a</sup>, Akira Monji<sup>a</sup>

<sup>a</sup>Department of Psychiatry, Faculty of Medicine, Saga University, Nabeshima 5-1-1, Saga 849-8501, Japan

<sup>b</sup>Department of Radiology, Faculty of Medicine, Saga University, Nabeshima 5-1-1, Saga 849-8501, Japan

<sup>c</sup>Department of Neuropsychiatry, Graduate School of Medical Sciences, Maidashi 3-1-1, Fukuoka 842-8582, Japan

**Corresponding author:** Hiroshi Tateishi, muutoyukainanakamatachi@gmail.com

and Monji Akira, amonji@hf.rim.or.jp

Address: 5-1-1 Nabeshima, Saga, Japan

E-mail: muutoyukainanakamatachi@gmail.com

Phone: +81-952-34-2304

Fax: +81-952-34-2048

**Abstract**

We herein report on a patient undergoing hemodialysis who developed various neuropsychiatric symptoms. The patient was a 62-year-old woman who began hemodialysis treatment for chronic kidney failure caused by chronic glomerulonephritis at 40 years of age. At 60 years of age, she began to show depressive symptoms such as insomnia, loss of appetite, and loss of motivation. About 1 month later, she became disorientated and often talked to herself or others in a rambling way, although her renal

function did not deteriorate. Her neuropsychiatric symptoms gradually ameliorated, and the bilateral occipital hypoperfusion detected by single-photon emission computed tomography improved. The diagnosis in the present case is discussed together with relevant literature on neurocognitive disorders in chronic kidney disease.

**Keywords:** chronic kidney disease (CKD); hemodialysis; neuropsychiatric symptoms; neurocognitive disorders

### **Introduction**

Chronic kidney disease (CKD) is a substantial public health problem. In the United States, almost 8% of the population has CKD and 571,000 patients receive treatment for end-stage renal disease (ESRD). Although the incidence of CKD is increasing in all age groups, this is particularly true in the elderly. Older adults are at greater risk of developing neurocognitive disorders and dementia, and a major determinant of quality of life in the elderly is the level of cognitive function. Recent data in this regard suggest that individuals at all stages of CKD may have a higher risk of developing dementia and cognitive impairment than those without CKD. Given the increase in life expectancy and the aging of the population in industrialized countries, the neurocognitive disorder burden associated with CKD is expected to worsen. Up to 70% of hemodialysis patients aged 55 years and older have moderate to severe chronic cognitive impairment, yet it is largely undiagnosed. Dementia is associated with high risks of death, dialysis withdrawal, hospitalization, and disability among patients with ESRD.<sup>1-5</sup>

We herein describe a case of a patient undergoing hemodialysis who developed various neuropsychiatric symptoms, and we review the relevant literature on neurocognitive

disorders in CKD.

### **Case report**

The patient was a 62-year-old woman with no family or individual history of mental or neurologic disorders. At 40 years of age, she began hemodialysis treatment for chronic kidney failure caused by chronic glomerulonephritis and started to develop hypertension. At about 58 years of age, she began to exhibit loud sleep talking at night. At 59 years of age, she started to develop lumbar spinal stenosis. At 60 years of age, she began to show depressive symptoms such as insomnia, loss of appetite, and loss of motivation. About 1 month later, she became disoriented and often talked to herself or others in a rambling way, although her renal function did not deteriorate.

She was admitted to our hospital to reduce her family's burden of care. Medical examinations, including complete blood count, C-reactive protein, electrolytes, and liver and thyroid function tests, but excluding renal function tests, such as blood urea nitrogen, creatine, and estimated glomerular filtration rate (eGFR), showed no clear abnormalities. Electroencephalography (EEG) showed an 8-Hz dominant alpha rhythm with an excessive 6–7-Hz theta rhythm, suggesting the presence of mild disturbance of consciousness. Neuroimaging studies revealed mild diffuse cerebral atrophy with an old small lacunar infarction in the right frontal lobe on magnetic resonance imaging (MRI), and bilateral occipital hypoperfusion on  $^{99m}\text{Tc}$ -ECD single-photon emission computed tomography (SPECT) (**Figure 1a**). There was no decrease in uptake of meta-iodobenzylguanidine (MIBG) by the left ventricle myocardium on MIBG scintigraphy. Her Mini-Mental State Examination (MMSE) scores fluctuated between 7 and 15 points. Her neuropsychiatric symptoms worsened further, and she began to

experience visual hallucinations and display psychomotor excitement and loitering.

She was diagnosed with delirium, and olanzapine was started at 5 mg/day. However, the olanzapine led to oversedation, although her psychomotor excitement and loitering disappeared. So olanzapine was discontinued. Donepezil was started at 1.5 mg/day and increased to 3 mg/day over 1 month. At 1 week following the initiation of donepezil, the patient exhibited a reduction in insomnia. At 3 weeks, her loss of motivation had improved. Within about 1 month, her appetite, disorientation, tendency to talk to herself or others in a rambling way, and visual hallucinations improved, her MMSE score was 26 points, and her EEG had normalized to a 9–10-Hz dominant alpha rhythm. After 2 months, her bilateral parieto-occipital hypoperfusion had improved (**Figure 1b**). Approximately 5 months later, her MMSE score was 29 points. The bilateral parieto-occipital hypoperfusion showed further improvement subsequently. She has been free of neuropsychiatric symptoms for more than 2 years to date.

## Discussion

### 1. Diagnosis of the present case

The patient was diagnosed with delirium for the following reasons. Her neuropsychiatric symptoms were associated with a disturbance of consciousness, as revealed by EEG as well as by remarkable fluctuation in her MMSE scores. Her psychiatric symptoms might have been ameliorated by donepezil, while they were worsened by olanzapine. Donepezil has been reported to be effective for the treatment of postoperative delirium.<sup>6</sup> However, there is no evidence from controlled trials showing that donepezil is effective in the treatment of delirium.<sup>7</sup> Additionally, cholinesterase inhibitors might lead to increased mortality when used to treat delirium.<sup>8</sup> It is possible that the delirium simply resolved

on its own, rather than as a result of the donepezil treatment. Previous studies on blood flow during delirium have shown more widespread hypoperfusion compared with that in the present case.<sup>9</sup> Improvement of visual hallucinations as well as occipital hypoperfusion or hypometabolism by donepezil has recently been reported in dementia with Lewy bodies (DLB).<sup>10,11</sup> Although the patient has been free of Parkinsonism and signs of autonomic disturbance thus far, her neuropsychiatric symptoms might be related to the pathology of Lewy body disease.<sup>12</sup> Delirium and DLB share a number of clinical similarities, and both cholinergic dysfunction and involvement of basal ganglia commonly exist in delirium and DLB.<sup>13</sup> It was recently reported that long-term administration of donepezil was well-tolerated in patients with DLB, and that the improvement in impaired cognitive function and psychiatric symptoms lasted for up to 52 weeks.<sup>14,15</sup> The present patient tolerated donepezil for 22 months without any known complications attributable to donepezil. The pharmacokinetics of donepezil do not appear to change in patients with moderately to severely impaired renal function.<sup>16</sup>

## **2. Neurocognitive disorders in CKD**

### **2.1. Cognitive impairment and dementia in CKD**

Most cross-sectional and longitudinal studies have suggested an association between cognitive impairment and CKD. A meta-analysis of cross-sectional and longitudinal studies comprising 54,779 participants yielded an association with cognitive decline in patients with CKD compared with patients without CKD (OR 1.65, 95% CI 1.32–2.05,  $p < 0.001$ , and OR 1.39, 95% CI 1.15–1.68,  $p < 0.001$ , respectively). CKD was reported to be a significant independent somatic risk factor for the development of cognitive decline.<sup>2</sup> CKD was also independently related to the risk of all-cause dementia in

patients with vascular risk factors in Japan.<sup>17</sup> Cognitive impairment is highly prevalent among hemodialysis patients and is associated with increased morbidity and mortality. Well-dialyzed hemodialysis patients with optimized hemoglobin levels and no history of stroke or dementia performed significantly worse on multiple measures of cognition compared with control subjects.<sup>5</sup> Recent studies have described a strong graded correlation between eGFR and cognitive function in CKD patients. The process of conventional hemodialysis may induce recurrent episodes of acute cerebral ischemia, which in turn may contribute to an acute decline in cognitive function during dialysis. Both symptomatic and occult subclinical ischemic cerebrovascular diseases appear to play large roles in a proposed model of accelerated vascular cognitive impairment in these populations. Severe cognitive impairment or dementia among hemodialysis patients is associated with approximately doubled risks for both mortality and dialysis withdrawal.<sup>3</sup> Compared with controls and patients with CKD in stage 3 and 4, stage 5 patients had lower scores ( $p < .05$ ) on measures of global cognitive function.<sup>18</sup>

## **2.2. Brain imaging in CKD**

Patients with CKD display a high prevalence of stroke. According to the United States Renal Data System, the prevalence is 17% for patients undergoing long-term hemodialysis, 10% for patients with mild to moderate CKD, and 4% in the non-CKD population, after accounting for age, sex, and race. A history of stroke doubles the risk for dementia in both CKD and non-CKD populations. Furthermore, CKD patients have an increased prevalence of subclinical cerebrovascular disease, with silent brain infarcts (SBIs), cerebral infarcts detected by brain imaging in the absence of clinical symptoms, more white matter lesions (WMLs), and more microbleeds.<sup>1</sup> Brain lesions in CKD

patients were first described in computed tomography-based studies. More than 30 years ago, Passer et al.<sup>19</sup> reported a high prevalence of cerebral atrophy in patients undergoing long-term hemodialysis. MRI has allowed a considerable increase in the rate of detection of subclinical cerebrovascular damage in CKD patients. It has been estimated that approximately half of patients with advanced CKD stages have SBIs, while the prevalence in the general population ranges from 8% to 28%. SBIs are associated with increased risks for stroke, cognitive decline, and incident dementia in CKD patients. The prevalence of WMLs is high (up to 70%) in both CKD patients and stroke patients. Most cross-sectional, population-based studies have shown strong associations of eGFR with white matter volume and WMLs. Similar to the case for SBIs, WMLs are predictors of increased incidences of stroke, dementia, and death. The incidence of cerebral microbleeds is higher in patients undergoing hemodialysis and also in patients with more moderate decreases in renal function. Interestingly, Watanabe<sup>20</sup> also found a high incidence of microbleeds in patients undergoing maintenance hemodialysis, but failed to find any correlation between duration of hemodialysis and prevalence of microbleeds. The author concluded that the high proportion of patients with microbleeds in this population was caused by other risk factors, possibly arterial hypertension and uremic toxins, rather than maintenance hemodialysis per se.<sup>1</sup>

## **2.3. Potential mechanisms**

### **2.3.1. Traditional risk factors**

The brain and kidneys have many common anatomic and vasoregulatory features. For example, they are low-resistance end organs exposed to high-volume blood flow and are thus susceptible to vascular damage. The present patient had a subclinical small



lacunar infarction, and thus her neuropsychiatric symptoms might have been related to this vascular pathology. The prevalence of traditional vascular risk factors, such as arterial hypertension, is higher in patients with CKD than in the general population. Furthermore, it has been suggested that vascular disease is a more likely cause of cognitive impairment than Alzheimer disease in this population. This hypothesis is supported by recently published data from the 3C study, in which faster eGFR decline (0.4 ml/min per 1.73 m<sup>2</sup> during the first 4 years of follow-up) was associated with global cognitive decline and incident dementia with a vascular component.<sup>21</sup> The contribution of cerebral vascular lesions to cognitive impairment in CKD patients is also supported by the pattern of cognitive disorders, and the prominent impairment of executive functions and psychomotor speed resembles the situation in stroke.

### **2.3.2. Nontraditional risk factors**

Nontraditional vascular risk factors, such as hyperhomocysteinemia, hypercoagulable states, inflammation, and oxidative stress, have also been linked to cognitive impairment.<sup>1</sup> Interestingly, elevated homocysteine levels are present in 85% of dialysis patients, but only 10% of the general population. In a prospective cohort study, plasma homocysteine was an independent risk factor for dementia.<sup>22</sup> Hyperhomocysteinemia has a direct prothrombotic effect on the vascular system, and thus may lead to both large and small-vessel disease. Elevated homocysteine levels are also associated with the number of WMLs and progression, possibly through direct endothelial damage or stimulation of an endothelial inflammatory response. Hyperhomocysteinemia can also impair neuronal pathways, because elevated homocysteine has a direct neurotoxic effect by activating the N-methyl-D-aspartate receptor or by conversion into homocysteic acid,

leading to cell death. Furthermore, clinical studies have shown that elevated plasma homocysteine concentrations are associated with an increased risk for Alzheimer disease. The vascular risk factors and brain abnormalities mentioned above can only partly explain the high frequency of vasculopathy-related cognitive disorder observed in CKD patients. Hence, other disease mechanisms are necessarily involved. First, chronic hypertension and numerous vascular risk factors are associated with an increased risk for Alzheimer disease. Conversely, the results of observational studies and clinical trials have suggested that antihypertensive drugs may decrease age-related cognitive decline and dementia. During the past decade, most studies have focused on the observation that the beneficial effects of various antihypertensive drugs in preventing cognitive decline and dementia are apparently not correlated with their blood pressure-lowering activity.<sup>1</sup> Moreover, the accumulation of uremic toxins may cause cerebral endothelial dysfunction and contribute to cognitive disorders in CKD. Various uremic toxins have been implicated in the pathogenesis of cognitive impairment. It has been reported that the cerebrospinal fluid and brain levels of some guanidine compounds, such as creatinine, guanidine, guanidinosuccinic acid, and methylguanidine, are substantially elevated in uremic patients. Interestingly, these high toxin concentrations (up to 10 times higher in CKD patients compared with control subjects) were found in brain regions that play determinant roles in cognition, such as the thalamus, mammillary bodies, and cerebral cortex. It is well-known that these uremic guanidine compounds are neuroexcitatory agents and have convulsant activity in animal studies.<sup>23</sup> Yaffe et al.<sup>24</sup> showed that community-resident elderly individuals with elevated levels of cystatin C (a cysteine protease inhibitor that colocalizes with  $\beta$ -amyloid in the brain of patients with Alzheimer disease) had lower cognitive test scores and were more likely to experience a

decline in cognitive function during a 7-year follow-up period, even after adjustment for vascular risk factors. Despite the absence of brain MRI data, it is possible that cystatin C has a direct effect on the risk of developing Alzheimer disease<sup>24</sup> (**Tables 1 and 2**).

### **2.3.3. Direct effects of hemodialysis**

Cerebrovascular disease, anemia, secondary hyperparathyroidism, uremic toxins, and dialysis disequilibrium syndrome have been reported as major causes of cognitive impairment that accompany CKD.<sup>25</sup> Dialysis disequilibrium syndrome is a clinical syndrome characterized by neurologic deterioration in patients who undergo hemodialysis. It is more likely to occur in patients during or immediately after their first treatment, but can occur in any patients who receive hemodialysis. The symptoms involve the neurologic system and are similar to those that occur in combination with increased intracranial pressure or acute hyponatremia, such as restlessness, headache, mental confusion, and coma. Animal experiments have clearly demonstrated that the rate of urea removal is crucial to the development of seizures and increased intracranial pressure.<sup>26</sup> Additionally, in one study, animals in a fast dialysis group were more likely to develop seizures and/or cerebral edema symptoms compared with those in a slow dialysis group. As long as the maximal safe rate for removal of urea remains unclear, it is critical to initiate hemodialysis with a low rate of urea removal.<sup>27</sup> Furthermore, the age of the dialysate and/or dialysis membrane is thought by some to affect a range of adverse effects associated with hemodialysis.

## Conclusions

We herein describe a case of a dialysis patient with various neuropsychiatric symptoms, together with a review of relevant literature on neurocognitive disorders. The neurocognitive disorders observed in CKD patients can probably be explained by the common susceptibility of brain tissue to vascular injury. The neuropsychiatric symptoms exhibited by the present patient appear to be mainly related to her vascular pathology. In addition to cerebrovascular causes, other potential mechanisms, such as direct neuronal toxicity of the uremic state, could be involved in CKD patients with neurocognitive disorders.

## References

1. Bugnicourt JM, Godefroy O, Chillon J-M, Choukroun G, Massy ZA: Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J Am Soc Nephrol* 2013;24:353–363
2. Etgen T, Chonchol M, Forstl H, Sander D: Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol* 2012;35:474–482
3. Murray AM: Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis* 2008;15(2):123–132
4. Tamura MK, Yaffe K: Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. *Kidney Int* 2011;79(1):14–22
5. Post JB, Morin KG, Sano M, Jegede AB: Increased presence of cognitive impairment in hemodialysis patients in the absence of neurological events. *Am J Nephrol* 2012;35:120–126
6. Gleason OC: Donepezil for postoperative delirium. *Psychosomatics* 2003;44:437–438

7. Overshott R, Karim S, Burns A: Cholinesterase inhibitors for delirium. *Cochrane Database Syst Rev* 2008;(1):CD005317
8. van Eijk MM, Roes KC, Honing ML, et al: Effect of rivastigmine as adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomized trial. *Lancet* 2010;376(9755):1829–1837
9. Soiza RL, Sharmab V, Ferguson K, Shenkin SD, Seymour DG, MacFullich AMJ: Neuroimaging studies of delirium: a systematic review. *J Psychosom Res* 2008;65:239–248
10. Mori T, Ikeda M, Fukuhara R, Nestor PJ, Tanabe H: Correlation of visual hallucinations with occipital rCBF changes by donepezil in DLB. *Neurology* 2006;66:935–937
11. Satoh M, Ishikawa H, Meguro K, Kusaya M, Ishii H, Yamaguchi S: Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with Lewy bodies: the Osaki-Tajiri project. *Eur Neurol* 2010;64:337–344
12. McKeith IG, Dickson DW, Lowe J, et al: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65:1863–1872
13. Gore RL, Vardy ERLC, O'Brien JT: Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? *J Neurol Neurosurg Psychiatry* 2015;86:50–59
14. Ikeda M, Mori E, Kosaka K, et al: Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: results from a 52-week, open label, multicenter extension study. *Dement Geriatr Cogn Disord* 2013;36:229–241
15. Mori E, Ikeda M, Kosaka K: Donepezil for dementia with Lewy bodies: a randomized,

placebo-controlled trial. *Ann Neurol* 2012;72:41–52

16. Tiseo PJ, Foley K, Friedhoff LT: An evaluation of pharmacokinetics of donepezil HCl in patients with moderately to severely impaired renal function. *Br J Clin Pharmacol* 1998;46(Suppl 1):56–60

17. Miwa K, Tanaka M, Okazaki S, et al: Chronic kidney disease is associated with dementia independent of cerebral small-vessel disease. *Neurology* 2014;82:1051–1057

18. Sánchez-Román S, Ostrosky-Solís F, Morales-Buenrostro LE, Nogués-Vizcaíno MG, Alberú J, McClintock SM: Neurocognitive profile of an adult sample with chronic kidney disease. *J Int Neuropsychol Soc* 2011;17(1):80–90

19. Passer JA: Cerebral atrophy in end-stage uremia. *Proc Clin Dial Transplant Forum* 1977;7:91–4

20. Watanabe A: Cerebral microbleeds and intracerebral hemorrhages in patients on maintenance hemodialysis. *J Stroke Cerebrovasc Dis* 2007;16(1):30–33

21. Helmer C, Stengel B, Metzger M, et al: Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. *Neurology* 2011;77(23):2043–2051

22. Seshadri S, Beiser A, Selhub J, et al: Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;346(7):476–483

23. De Deyn PP, Vanholder R, Eloot S, Glorieux G: Guanidino compounds as uremic (neuro)toxins. *Semin Dial* 2009;22(4):340–345

24. Yaffe K, Lindquist K, Shlipak MG, et al: Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. *Ann Neurol* 2008;63(6):798–802

25. Watanabe K, Watanabe T, Nakayama M: Cerebro-renal interactions: impact of uremic toxins on cognitive function. *Neurotoxicology* 2014;44:184–193

26. Arieff AI, Massy SG, Barrientos A, Kleeman CR: Brain water and electrolyte metabolism in uremia: effects of slow and rapid hemodialysis. *Kidney Int* 1973;4:177–187
27. Zepeda-Orozco D, Quigley R: Dialysis disequilibrium syndrome. *Pediatr Nephrol* 2012;27:2205–2211

### Figure legends

**Figure 1. Changes in blood flow shown on SPECT imaging during treatment with donepezil. (a–d)**  $^{99m}\text{Tc}$ -ECD SPECT images before (a) and at 2 months (b), 9 months (c), and 22 months (d) after the administration of donepezil. The SPECT images demonstrate a remarkable decrease in blood perfusion in the bilateral parieto-occipital lobes before the administration of donepezil (a). This decrease gradually disappears following the administration of donepezil (b–d).

**Table 1. Uremic compounds with adverse effects**

---

on brain function cited from Ref. 25

Uremic compounds	Normal concentration (SD)	Uremic concentration* (SD or range)
Homocysteine (mg/L)	1.35 (0.14)	9.73 (2.05)
Guanidinosuccinic acid (mg/L)	0.03 (0.01)	1.43 (0.99–1.72)
Methylguanidine (µg/L)	<7.3	139.4 (72.3–218.3)
Cystatin C (mg/L)	<1.6	22.9 (9.0)

\*Uremic concentration refers to the plasma concentration from ESRD (hemodialysis or peritoneal dialysis) patients.

**Table 2. Risk factors for neurocognitive dysfunction in CKD cited for Ref. 1**

Risk factors for neurocognitive dysfunction in CKD

---

Arterial hypertension

---

Uremic compounds

---

Hypercoagulable states

---

Inflammation

---

Oxidative stress

---



