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Cognitive Impairment in the Aging Dialysis and Chronic Kidney Disease Populations: an Occult Burden

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Abstract

The heavy burden of cognitive impairment in hemodialysis and chronic kidney disease patients has only recently become recognized. Up to 70 percent of hemodialysis patients ages 55 years and older have moderate to severe chronic cognitive impairment, yet it is largely undiagnosed. Recent studies describe the strong graded relation between estimated glomerular filtration rate (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 acute decline in cognitive function during dialysis. Thus the worst time to communicate with dialysis patients may be during the hemodialysis session. Both symptomatic and occult, subclinical ischemic cerebrovascular disease appear to play a large role in a proposed model of accelerated vascular cognitive impairment in these populations. Severe cognitive impairment or dementia among hemodialysis patients is associated with an approximately two-fold increased risk of both mortality and dialysis withdrawal. Pre-dialysis cognitive screening and adding dementia to the list of comorbidities on Form 2728 would provide critical information regarding the benefit versus risks of receiving dialysis. It could also improve quality of care and outcomes by raising clinician's awareness of the potential effects of cognitive impairment on medication, fluid, and dietary compliance, and ability to make advance directive decisions among dialysis patients. While much remains to be learned regarding the pathophysiology of cognitive impairment in kidney disease, the public health implications of this substantial burden are immediate.

Keywords

cognitive impairment; delirium; dementia; hemodialysis; CKD

Introduction

The heavy burden of cognitive impairment in hemodialysis and chronic kidney disease (CKD) patients has only recently become recognized. This review summarizes the state of knowledge

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regarding the epidemiology and pathophysiology of acute and chronic cognitive impairment in these populations. The intent is to provide an update to the excellent summary of the epidemiology of cognitive function in dialysis patients by Pereira and co-workers in 2005 (1). While much remains to be learned regarding the multiple causes of cognitive impairment in these populations, the health policy implications of this substantial burden are immediate.

For the purposes of this review, severe cognitive impairment will be considered as approximately equivalent to dementia, which per DSM IV criteria is defined as chronic cognitive impairment in two or more cognitive domains that substantially affects daily function, represents a decline in pre-morbid function, and is not due to concomitant acute delirium (2,3)

Prevalence of Cognitive Impairment in Hemodialysis Patients

Early studies among small samples of hemodialysis patients reported moderate rates of cognitive impairment across multiple cognitive domains, but often excluded older patients or those with stroke or severe comorbid conditions (4–8). One 1997 study using the relatively insensitive Mini Mental State Exam (MMSE) found that 30 percent of 336 hemodialysis patients aged 23 to 93 years had mild to severe cognitive impairment, using very conservative cut-points (9).

Two recent studies describe the high prevalence of cognitive impairment in CKD and hemodialysis patients (2,10). In a study of CKD and hemodialysis patients by Kurella and colleagues, among 80 hemodialysis patients (mean age 61.2 years), 38 percent had severe impairment in executive function and 33 percent severe memory impairment (10). We found very similar results in our recent study of 338 hemodialysis subjects. Using a detailed 45 minute neuropsychological battery, 37 percent of subjects had severe, 36 percent moderate, and 14 percent mild cognitive impairment; only 13 percent had normal cognitive function. Hemodialysis patients were more than three times as likely to have severe cognitive impairment than a comparison group of non-CKD patients. However, clinical awareness of the diagnosis was poor; cognitive impairment was only documented by medical record in 2.9 percent of the cohort.

Cognitive Impairment in Chronic Kidney Disease Patients

Among Stage 3–4 CKD patients in Kurella's study above, 23 percent had severely impaired executive function and 28 percent scored poorly on delayed memory (10). Multiple studies report a cross-sectional, graded relation between eGFR level and cognitive function (10–12). In the Heart, Estrogen/Progesterone Study among menopausal women, each 10- mL/min/1.73 m² decrement in eGFR corresponded to an approximately 15 percent to 25 percent increase in risk for cognitive dysfunction among individual cognitive domains (11).

There is also evidence for a longitudinal relation between baseline eGFR and cognitive decline. The Health and Aging Body Composition Study, using the Modified Mini Mental State exam (3MS), showed a significant, graded risk for cognitive decline or dementia with CKD at baseline. For eGFR 45 to 59 mL/min per 1.73 m² the AOR for cognitive decline was 1.32, compared to 2.43 for a eGFR less than 45. In the Cardiovascular Health Study, moderate kidney insufficiency (creatinine > 1.5 mg/dL in men, > 1.3 mg/dL in women) was associated with a 37 percent increased risk of incident dementia over 6 years of follow-up among the 84 percent of subjects who reported good-excellent health (13). Shared cardiovascular risk factors however may explain some of the association between severity of CKD and burden of cognitive impairment and do not prove cause and effect.

Cognitive Impairment is Under-diagnosed in CKD and Hemodialysis Patients

According to the 2006 USRDS annual data report (ADR) using Medicare claims data, the prevalence of dementia is slightly higher in the CKD cohort than the hemodialysis cohort, at 7.6 percent, compared to 7 percent, respectively. It increases with age to 16.8 percent among those 85 years and older in the CKD cohort, compared to 11.0 percent in the hemodialysis cohort (14). Although more studies of the prevalence of cognitive impairment in these patients populations are needed, several suggest it is largely undetected by clinicians. In Sehgal's study above of 336 hemodialysis patients, only 15 percent of the cognitively impaired patients (MMSE <24) had a medical record diagnosis of cognitive problems. Whereas the prevalence of severe cognitive impairment was 37 percent in our primary collection study and almost identical in Kurella's study, the prevalence of dementia using Medicare claims-based data from the USRDS is only 7 percent, or 1/5 of probable dementia cases (15). Our study cohort was representative of the USRDS cohort, except there were fewer non-whites (47.6% in the USRDS vs. 18.7% in our cohort); since severe cognitive impairment was more common in the non-whites, the prevalence may actually be higher. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), only 4 percent of the hemodialysis population carried a medical record diagnosis of dementia (16). Thus, many cases may go unrecognized, raising the specter of a massive occult burden of cognitive impairment in CKD and hemodialysis patients (16).

Risk Factors for Cognitive Impairment in Hemodialysis Patients

In community-based studies among the general population, older age, female gender, low education, race and ethnicity, diabetes, hypertension, lipids, stroke, anemia, history of head trauma, mid-life obesity, inflammatory factors, the APOE4 allele and other genetic markers have been identified as risk factors for Alzheimer's disease or vascular cognitive impairment in community-based studies of the general community population (17–23). Dietary intake (fruits, vegetables, Omega 3's, Mediterranean diet) and physical activity appear to be protective, and hormone replacement therapy and homocysteine are still controversial; there is also an interactive effect between some risk factors and the APOE-4 allele (24).

Hemodialysis and CKD populations share most of these same risk factors for cognitive impairment. However, in contrast to the general population, the roles of aging and non-vascular factors are overshadowed by stroke and the high prevalence of cardiovascular risk factors (18–20). In addition, the contributions of factors secondary to kidney failure such as uremia, anemia, metabolic disturbances and hemodynamic instability during dialysis are still to be defined (4,25). In the Health ABC study, CKD accounted for approximately 10 percent of the cognitive impairment risk that was unexplained by demographic factors and comorbidities (26). In the DOPPS, age, race, stroke, diabetes low education, anemia and measures of malnutrition were independently associated with dementia (16). Similar measurable risk factors have been identified in analyses in the USRDS CKD and hemodialysis populations (14). Stroke, low education and an equilibrated Kt/V ≥ 1.2 were associated with severe cognitive impairment in our study of 338 hemodialysis patients.

Most hemodialysis patients are vasculopathies, with high rates of hypertension (80%), diabetes (60%) (14), markedly elevated levels of inflammatory markers and homocysteine (27), vascular endothelial dysfunction (28), cardiovascular events including stroke (29,30), and carotid atherosclerosis (31), all of which contribute to vascular cognitive impairment (23) and neurodegenerative diseases such as Alzheimer's disease (18,32). Ischemic cerebrovascular disease and underlying vascular endothelial pathology however appear to play the largest roles in the genesis of cognitive impairment in CKD and hemodialysis patients.

Stroke in the CKD and Hemodialysis Populations: the Unspoken Burden

Despite remarkably high rates of stroke, surprisingly little has been written about the impact of stroke on the CKD and dialysis populations. The prevalence of stroke in the United States Renal Data System (USRDS) hemodialysis population is 17 percent, and 10 percent among CKD patients, compared to 4 percent in the general Medicare population (14). The proportion that experience a stroke each year is almost as high; the incidence is 15 percent for hemodialysis patients and 9.5 percent for CKD patients, compared to 2.4 percent in the non-CKD population. Stroke is also 6 to 9 times more common in hospitalized hemodialysis patients than in non-dialysis patients (33). A history of stroke doubles the risk of dementia in both the non-CKD and hemodialysis populations (2,14,34)

Subclinical Cerebrovascular Disease: Silent Infarcts and White Matter Disease

In addition to clinically evident acute stroke, hemodialysis patients are at increased risk for subclinical cerebrovascular disease (35), manifested by silent or asymptomatic strokes, and white matter disease, or leukoariosis. Silent strokes are diagnosed on brain magnetic resonance imaging (MRI) as infarcts. White matter disease is represented by hyperintense signals on T2-weighted images in the subcortical white matter. Both are linked to cognitive and physical function decline in the general population, and both are very common in CKD and dialysis patients (35).

Silent strokes occur in up to 33 percent of the older community population (36), or 5 times more common than symptomatic strokes (37). Among CKD patients, the prevalence of silent infarcts is inversely reported to kidney function as measured by cystatin C in the Cardiovascular Health Study (38); among hemodialysis patients in another study, the prevalence was 49 percent, or 5 times more common than in control subjects (39). Silent strokes are associated with increased risk of subsequent clinically evident stroke, cognitive and physical decline, and incident dementia (36,37,40) in both the general and CKD/dialysis populations (39,41).

Although previously the subject of much debate, white matter disease is now believed to most likely represent microvascular disease due to chronic hypoperfusion. One recent study found strong correlations between ultrastructural hypoxic and ischemic neuropathologic findings in white matter on autopsy and white matter disease on brain MRI's performed in 465 post-mortem subjects (42). White matter disease may be of greater clinical significance than cortical infarcts; amount of white matter disease correlated more strongly with severity of cognitive impairment than size or number of infarcts in one recent study of patients with vascular dementia (43).

CKD and hemodialysis patients have high rates of white matter disease (44–47), and in one recent study among peritoneal dialysis patients, 68 percent had substantial white matter disease, compared to only 17.5 percent among non-CKD controls (48). In the Rotterdam (49) and Cardiovascular Health Studies (CHS) (50) white matter disease was associated with deficits in the cognitive domains of executive function and processing speed more than deficits involving cortical cognitive domains such as memory loss and verbal skills, suggesting a subcortical, vascular pattern of cognitive impairment.

Acute Cognitive Impairment During Dialysis: Delirium

Delirium is an acute confusional state affecting global cognition that occurs in up to 30 percent of hospitalized elderly (2,51). It is characterized by an acute disturbance of consciousness, with decreased ability to maintain attention; cognitive changes such as memory deficits,

disorientation, or language disturbance; reversed sleep-wake cycles; and at times delusions or hallucinations (3). Classical teaching holds that delirium is reversible, but recent studies have refuted this teaching. In delirious hospitalized elderly patients, delirium is associated with both long-term cognitive and physical function decline, leading to a loss of ability to perform on average one activity of daily living (52–54).

Dementia, or chronic cognitive impairment, is in turn associated with increased risk of delirium, because it is believed to represent a state of low brain reserve, susceptible to acute insults (55,56). The confusion induced by cerebral edema due to the acute fluid, urea, and electrolyte shifts during dialysis (especially among newly initiated hemodialysis patients) is one of the symptoms classically referred to in the “dialysis disequilibrium,” syndrome. These symptoms appear to be consistent with the Diagnostic and Statistical Manual Fourth Edition (DSM-IV) definition of delirium (3,57). Thus, the potential exists for the repetitive insult of dialysis to induce recurrent delirium and thereby substantially increase the risk of dementia.

In addition to cerebral edema, acute cardiovascular dynamic changes during the dialysis process may contribute to acute confusion or delirium. Rapid fluctuations in blood pressure, the removal of large fluid volumes, and hemoconcentration increase the risk of inducing cerebral hypoperfusion (58). The recent use of high flux dialysis membranes enables shorter sessions for a given prescribed dose, but also increases the potential for more rapid osmotic shifts. The shortened dialysis time in turn leads to greater risk of hemodynamic instability.

The degree to which acute hemodynamic changes and fluid shifts may also induce acute inflammatory and degenerative changes is unknown. However, one recent study in cardiopulmonary bypass patients, who are also subject to acute declines in cerebral perfusion, suggests a possible corollary to the effects of dialysis on the brain. Among patients with symptoms of acute cognitive decline at 6 hours and 3 months after surgery, markers of neurodegenerative disease (tau protein and neuron specific enolase) and inflammatory factors such as C reactive protein were significantly elevated after cardiopulmonary bypass surgery compared to before surgery (59,60), but not among bypass patients without acute cognitive decline.

Acute Decline in Cognitive Function During Hemodialysis

Acute hemodynamic changes and large fluid shifts during dialysis may increase the risk of acute changes in cognitive function during dialysis, or delirium. Our group sought to determine to what extent cognition varies over the 2 day dialysis cycle by conducting cognitive testing at four times during the dialysis cycle (before, during, after, and the day after dialysis) among 28 hemodialysis subjects with a mean age of 66.7 years and mean dialysis vintage of 44.7 months. Global cognitive function varied significantly over the dialysis cycle. On average it was best on the day after dialysis or immediately before the dialysis session, plummeted during dialysis, and substantially recovered an hour after dialysis.

Previous studies of variation in cognitive function were conducted in small samples by measuring cognitive function at 2 or 3 times over the 2 day dialysis cycle. Most found that optimal cognitive function occurred 24 hours after dialysis, but worsened at times further out from the last dialysis run (7,61). None however measured cognition at four points over the dialysis cycle, including during dialysis.

Although further studies are needed to confirm our findings, our results suggest that the worst time to communicate with dialysis patients appears to be during the hemodialysis session. Currently, the Centers for Medicare and Medicaid Services (CMS) only reimburses for hemodialysis visits during dialysis, but confusion during dialysis could contribute to subsequent medication errors, dietary and fluid noncompliance, and avoidable hospitalizations.

Clinical assessment and discussions regarding medication changes or advance directives may be better held on the off day, shortly before the dialysis run, or an hour or more afterward. CMS may need to review current monthly reimbursement rules to allow visits at these times to maximize communication and patient compliance. Maintaining stable cognitive function using gentler, less efficient dialysis treatment options, such as peritoneal or daily dialysis, may be more important than rapidly achieving a lower urea.

The Pathophysiology of Cognitive Impairment in Hemodialysis Patients: An Accelerated Model of Vascular Dementia

The natural history of cognitive impairment in dialysis patients likely begins years before CKD progresses to ESRD. This is suggested by the recent studies noted above that report strong cross-sectional and longitudinal relations between eGFR and cognitive function in CKD patients (10–13).

Vascular cognitive impairment or mixed vascular cognitive impairment and Alzheimer's disease appear to be much more common in hemodialysis patients than Alzheimer's disease alone (62–64). As noted above, the incidence of stroke in hemodialysis patients is at least 15 percent. Systemic microvascular disease due to diabetes, hypertension, and elevated inflammatory factors involving both the renal and cerebral vasculature are a potential uniting mechanism in the natural history of cognitive impairment in CKD and hemodialysis patients (62,63,65). It may be helpful to use the paradigm of end-organ disease to describe a model of vascular cognitive impairment in CKD and dialysis patients. In diabetics the retina is an end-organ with microvascular disease manifested as retinopathy, and is associated with a marked progression of cerebral small vessel disease, white matter disease and incident lacunar infarcts. The degree of microvascular disease in the renal vasculature and secondary microalbuminuria in turn may reflect a similar level of microvascular disease in the brain (66–68).

Microalbuminuria is associated with cerebral small vessel disease in community-based elderly subjects (69), and with subclinical atherosclerosis in the Cardiovascular Health Study (70). In the kidney as end-organ, microvascular disease is manifested by nephrosclerosis, secondary leaky glomeruli and proteinuria. With the brain as end-organ, disruption of the blood/brain barrier due to microvascular disease may play an analogous role, with damaged vascular endothelial tight junctions causing leakage of protein, potentially contributing to white matter disease and pre-amyloid oligomers (62,71,72).

Patients with white matter disease, lacunar infarcts, and microbleeds have evidence of disrupted blood/brain barrier on brain imaging studies, as reflected by an increased cerebrospinal fluid (CSF)/plasma albumin ratio, a marker of blood/brain barrier disruption (63,64). Progression of Alzheimer's disease is accelerated in patients with elevated CSF/plasma albumin ratio (65).

These findings lead to the key underlying question: how much of the cognitive impairment observed in hemodialysis patients is: a) pre-existing, due to uremia, high rates of stroke and microvascular disease, and neurodegenerative disease, b) due to the dialysis process itself, and c) attributable to the intermittent uremia and metabolic disturbances associated with end stage renal failure?

The Dialysis Process and Cognitive Impairment

The dialysis process may directly contribute to cognitive impairment by inducing recurrent cerebral ischemia. That the dialysis process may actually induce strokes is suggested by multiple brain imaging studies. In a Japanese study of 151 hemodialysis patients with acute

stroke, 34 percent of infarcts occurred during or less than 30 minutes after a dialysis session (73). Vertebrobasilar infarcts were also more common in hemodialysis patients than in patients with normal kidney function (48% vs. 33%, $p < 0.05$), possibly reflecting preferential ischemia in watershed areas more susceptible to acute hypovolemia during dialysis. The number of hypotensive episodes during dialysis also correlates with degree of frontal cerebral atrophy, a sequelae of recurrent strokes (74).

Significant decreases in cerebral perfusion and blood flow velocity after dialysis compared with before the session have been documented using Xenon inhalation scans of cerebral circulation (75) and transcranial Doppler ultrasound of the carotid, basilar, and middle cerebral arteries (76–78). Positron emission tomography (PET) scans also show decreased cerebral oxygen metabolism and regional blood flow in hemodialysis patients; cerebral blood flow in the frontal lobes and white matter is inversely related to dialysis vintage (79).

We found that cerebral function declined acutely during dialysis (25). The acute fluid shifts and intravascular volume loss that occur during dialysis induce cerebral edema and decreased intra-cerebral blood pressure, blood velocity and cerebral perfusion (76–78). If these hemodynamic factors increase the risk of recurrent transient ischemic accident and stroke, that risk may rise with the dialysis dose (Kt/V). We found that equilibrated $Kt/V > 1.2$ was associated with severe cognitive impairment in our study of the prevalence of cognitive impairment in hemodialysis patients. Whether reducing the rate (K) of clearance through longer but slower dialysis might reduce the risk of cerebral edema and recurrent ischemic episodes during dialysis, and in turn contribute to lower rates of severe cognitive impairment, needs further exploration.

The effect of dialysis modality on risk of cognitive impairment is unclear. Based on USRDS data, dementia appears less common among peritoneal dialysis patients than hemodialysis patients (15). However, future studies are needed to differentiate between modality as a risk factor from the factors contributing to selection bias among patients choosing peritoneal dialysis over hemodialysis (15). One recent study of young hemodialysis patients (mean age 39.6 years) showed that patients who transitioned to daily nocturnal dialysis achieved improved cognitive outcomes in attention, processing speed, and working memory after 6 months (80). These same cognitive domains are among those most affected by vascular cognitive impairment (43); thus some of the reversible cognitive deficits may be secondary to improved cerebral perfusion. Daily dialysis, with less acute hemodynamic changes, may offer a gentler alternative for the cerebral circulation, although it is not an option for some patients.

Model of the Pathophysiology of Accelerated Vascular Cognitive Impairment in Hemodialysis Patients

The model in Figure 1 describes the interaction between many of the chronic and acute factors believed to contribute to the pathophysiology of cognitive impairment in hemodialysis patients. Chronic factors contributing to low brain reserve are found on the left, such as pre-existing stroke, atrophy, blood/brain barrier disruption, and cardiovascular risk factors present in most late-stage CKD and newly initiating hemodialysis patients. Acute insults are described on the right, such as cerebral edema and hypoperfusion secondary to recurrent dialysis, infection, congestive heart failure, arrhythmia, and other events. Together, the acute factors interacting with the chronic baseline low brain reserve are a lethal combination, leading to high rates of moderate to severe cognitive impairment. Brain autopsy studies are needed to further disentangle this complex pathophysiology.

Outcomes of Cognitive Impairment in CKD and Hemodialysis Patients

Dementia is associated with an increased risk of multiple adverse outcomes. Prevalent dementia in hemodialysis patients increases the risk of hospitalization (unadjusted HR 1.8) in the USRDS population (15). One USRDS study found that compared to those without dementia, CKD patients with a history of dementia had an average life span after dialysis initiation of 1.09 vs. 2.7 years ($p < 0.001$), with an adjusted HR of 1.9 (81). In another USRDS analysis, dementia vs. no dementia was associated with a greater risk of death in CKD patients than among hemodialysis patients (HR of 2.26 vs. 1.86, respectively) (14). Among hemodialysis patients in DOPPS, dementia was associated with a 1.48 fold increased risk of death over one year, but with a HR of 2.0 for dialysis withdrawal (16). Dementia also increases costs of care; in 2002 approximately \$19,100 more Medicare dollars were spent over one year in hemodialysis patients with dementia compared to those without (15).

Health Policy Implications

Currently, neither a cognitive history nor assessment is required at dialysis initiation or anytime during maintenance dialysis. Dementia is also not listed as a comorbid condition on the CMS Medical Evidence Report (CMS-2728), required at dialysis initiation for Medicare entitlement. Given the high rate of stroke and severe cognitive impairment in hemodialysis and CKD patients, many may lack adequate judgment to weigh the benefits vs. risks of initiating hemodialysis, or to withdraw from dialysis once initiated. Among our cohort of 338 hemodialysis patients, 28 percent of those with severe cognitive impairment had been on dialysis for less than one year (2).

The nephrology community is reexamining the appropriateness of initiating dialysis in older patients with a high risk of poor outcomes, given their high rates of hospitalization and mortality and frequent low quality of life (see accompanying article by Germain M in this issue). Of the deceased hemodialysis patients in the USRDS 2001 to 2002 cohort, ($n = 115,239$), approximately 22 percent chose to withdraw from dialysis. Failure to thrive was the most common reason for dialysis withdrawal, identified in 42.9 percent of patients (82). Failure to thrive is a poorly defined term that usually denotes unintentional weight loss, functional dependence, depression, and confusion (83), but these symptoms also occur in patients with moderate to severe dementia. Thus, patients who may be demented at dialysis withdrawal might have been identified as poor hemodialysis candidates prior to initiation.

These factors, along with the high prevalence of cognitive impairment in CKD and hemodialysis patients, warrant a screening cognitive assessment for all patients considering long-term maintenance dialysis in non-acute settings. Specifically, the following recommendations could be considered for stages 4–5 CKD patients: 1) require a pre-dialysis initiation and annual CMS-reimbursed cognitive screen performed by a technician, 2) if the patient scores below the cutpoint on the screening test, require a referral for a detailed cognitive assessment by a neurologist, psychiatrist, or geriatrician to evaluate them for dementia, and 3) include dementia as a comorbidity choice on CMS Form 2728.

Conclusion

The heavy burden of cognitive impairment in CKD and hemodialysis patients is now apparent. Ischemic cerebrovascular disease and underlying microvascular pathology appear to play a large role in the pathophysiology, but further elucidation of the multiple complex causes are needed. The process of conventional hemodialysis may induce recurrent episodes of acute cerebral ischemia and acute delirium during dialysis. Increased awareness among clinicians of the effects of cognitive impairment on daily function, quality of life, and medication, fluid, and dietary compliance is needed. Changes in current CMS policy regarding pre-dialysis cognitive

assessment and reimbursement for dialysis care visits should be considered. Doing so would improve physician awareness of the presence of cognitive impairment and assist the patient and family in their decisions to initiate or withdraw from dialysis.

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Figure 1.
 Model of the Pathophysiology of cognitive impairment in hemodialysis patients.