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Cognitive Impairment in CKD: No Longer an Occult Burden

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Until recently, cognitive impairment and its negative outcomes in chronic kidney disease (CKD) patients were largely neglected by clinicians and the academic community. Cognitive impairment was described as an occult burden, highly prevalent in CKD and end-stage renal disease (ESRD) patients and associated with multiple negative outcomes, but unacknowledged as a significant public health burden.^{1–3} However, several recent studies have reported a high association with increased mortality. The study by Griva et al⁴ in this issue of the *American Journal of Kidney Diseases* adds to the evolving story of cognitive impairment in kidney disease by measuring mild and more severe cognitive impairment in hemodialysis and peritoneal dialysis patients.

The authors report a broad range of cognitive impairment in fully two-thirds of an urban cohort of 145 younger peritoneal dialysis, home hemodialysis, and in-center hemodialysis patients in London, United Kingdom.⁴ They define mild and moderate cognitive impairment as performing 1–1.99 and 2–2.99 standard deviations (SD) below age-adjusted population norms, respectively. Patients were classified as cognitively impaired if they performed in the mild or moderately impaired range on at least 2 tests in the comprehensive cognitive battery. By this unusual definition, cognitive impairment more than doubled the risk of death in the cohort, which was followed for an average of approximately 5 years. The strongest predictors of mortality were cognitive impairment, diabetes, and physical component score on the Medical Outcome Study Short Form Health Survey (SF-36, higher score was protective). Age was likely not a factor due to the young age of the study group.

This is not the first time that a strong relation between cognitive impairment and mortality in ESRD patients has been reported. Previous studies in hemodialysis patients have reported hazard ratios (HRs) for mortality associated with dementia in the range of 1.5–2.2.^{1,5–7} However, most previous studies were conducted in older cohorts of predominantly in-center hemodialysis patients, did not include peritoneal dialysis patients, and examined dementia, the diagnostic equivalent of severe cognitive impairment, as the predictor of mortality. In contrast to Griva et al, the previous investigators did not measure mild cognitive impairment. The finding of a strong association between a broad range of cognitive impairment and mortality despite the young mean age of 50 years, in a cohort of 47% peritoneal dialysis patients, further distinguishes this study from previous ones.

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The strong association of cognitive impairment and mortality found in this and in previous studies puts cognitive impairment on equal or stronger footing as compared to other clinical predictors of mortality in dialysis patients, such as stroke, myocardial infarction, and cardiac arrhythmias.^{7,8} Dementia in dialysis patients also increases risk of hospitalization almost 2-fold (HR, 1.8)⁹; hospitalization in turn contributes to higher mortality. Both negative outcomes likely occur in part because without supervision, patients with cognitive impairment are unable to adhere to medication regimens and dietary restrictions related to hypertension, diabetes, and congestive heart failure, and are less likely to comply with dialysis schedules.

About 50% of individuals in the Griva et al study cohort were cognitively impaired in executive function (Trail Making Test part B) and verbal memory (Rey Auditory Verbal Learning Test, evenly split between mild and moderate impairment). The high frequency of cognitive impairment is not dissimilar to previous reports of 30%–70% in hemodialysis patients,^{2,10,11} but these studies did not measure mild impairment. Further, only the Frequent Hemodialysis Network Trials included many younger patients (ages 21–85 years), with a similar mean age of 51.6 years.¹⁰

Recent studies in CKD patients suggest that the natural history of cognitive impairment begins before transition to ESRD, and that there is a strong graded relation between declining estimated glomerular filtration rate (eGFR) and cognitive function.^{11–14} Below the eGFR threshold of 45 mL/min/1.73 m² (stage 3B CKD, 0.75 mL/s/1.73 m²), risk of cognitive impairment more than doubles (odds ratio, 2.43) compared with higher eGFR. Approximately one-fourth of such patients have at least moderate cognitive impairment.^{13,14} This suggests that once kidney function is reduced by more than half, cognitive reserve is also likely depleted and should be assessed.

The implication of results reported by Griva et al and other recent studies is that clinicians need to adjust their antennae to cognitive impairment. It is a serious comorbid condition for which screening is warranted for stage 3 CKD and higher, and ESRD patients of all ages.^{2,6,14,15} Cognitive impairment often leads to decreased medication and dietary adherence, and to increased risk of secondary iatrogenic hospitalizations and death. Identifying patients with cognitive impairment could help clinicians and families design treatment plans to supervise medication administration and diet and care plans, and to hold appropriate discussions regarding initiating and withdrawing from dialysis. Identification could also substantially decrease costs of care for these patients; in the 2002 United States Renal Data System (USRDS) dialysis population, more than \$19,100 additional Medicare dollars were spent over 1 year for hemodialysis patients with dementia than for those without.¹⁶

To screen for cognitive impairment, either the Montreal Cognitive Assessment tool (MoCA),¹⁷ a newer test, or the Mini-Mental State Exam (MMSE),¹⁸ a less-sensitive instrument widely used in primary care, could be used by clinicians caring for CKD and ESRD patients. The MoCA is an excellent instrument that is free, downloadable from the internet,¹⁹ and easily administered by nonprofessional trained assistants in about 10 minutes, similar to the MMSE. It has been used for screening in large observational and clinical trials,^{20,21} including the current National Institutes of Health Systolic Blood Pressure Intervention Trial (SPRINT), in which a subsample of the cohort will be stage 3 CKD patients. The MoCA measures performance in the cognitive domains most important for daily function: (1) executive function (attention and decision-making skills), (2) verbal memory, (3) language, and (4) visual-spatial skills. Its sensitivity is 90% for detecting mild cognitive impairment and 100% for detecting dementia, compared with 18% and 87% for the MMSE. A score <26 on the MoCA indicates at least mild cognitive impairment and suggests that medication supervision and help with decision-making are needed; the mean score for dementia is 16, but the addition of functional impairment to a score <26 is indicative of dementia.

Nephrologists are often understandably hesitant to attempt predicting survival in dialysis patients and initiating end-of-life care discussions. The study by Griva et al and other studies cited point to dementia as a strong predictor of mortality in dialysis patients, and add another piece of clinical information to aid in these discussions. Importantly, a recent prognostic tool with strong validity was developed to predict 6-month survival in dialysis patients.⁶ The strongest of the 5 prognostic factors was the following so-called Surprise Question: “would I be surprised if this patient died within the next 6 months?” (adjusted HR, 2.71; 95% confidence interval [CI], 1.76–4.17). Dementia was next strongest (HR, 2.24; 95% CI, 1.11–4.48), followed by older age (HR for 10-year increase, 1.36; 95% CI, 1.17–1.57), peripheral vascular disease (HR, 1.88; 95% CI, 1.24–2.84), and decreased albumin (HR for 1-U increase, 0.27; 95% CI, 0.15–0.50). It would seem wise to take advantage of this prognostic tool to improve end-of-life care for dialysis patients by providing more accurate prognostic information to them and their families.

The strongest limitation of the study by Griva et al is the very high survival rates of the study cohort compared with the US ESRD population, introducing substantial survival bias to the data. The mean 5-year survival rate is 50% for incident USRDS hemodialysis patients with mean age 50 years, 29% for ages 65–74 years, and 14% for ages 75 years and older.²² As mean ESRD duration was almost 4 years for this cohort, and patients were followed on average for an additional 5 years, this is truly a remarkably healthy cohort. The small sample size in a cohort that included peritoneal dialysis, home hemodialysis, and in-center hemodialysis patients reduced the power of the analyses to measure risk factors for mortality, and to generalize the results to dissimilar dialysis cohorts. The cohort also includes unknown numbers of patients who must have failed transplants, because mean number of months on renal replacement therapy is greater than mean dialysis duration. As the distribution of cognitive impairment by dialysis modality is not provided, results cannot be directly compared to studies of peritoneal dialysis or hemodialysis patients. Frequency of cognitive impairment and of mortality may have been underestimated because patients with history of stroke were excluded. Stroke doubles the risk of severe cognitive impairment and mortality in dialysis patients.^{2,7}

The authors state that they found a significant association between mild to moderate cognitive impairment and mortality, but their definition of mild to moderate includes performance 1–2.99 SD below age-adjusted population norms on at least 2 tests in their comprehensive battery. A performance level >2 SD below norms in 2 or more cognitive domains is usually classified in neurologic studies as severe cognitive impairment. Thus, it is likely that despite patients with dementia supposedly being excluded from the study, a substantial proportion of patients had severe cognitive impairment, or dementia. In addition, some patients with dementia may not have been excluded using the medical record and nephrologist diagnoses of dementia. However, the strength of the association between cognitive impairment and mortality was so strong (HR, 2.5) that the validity of the association is not in question.

Despite these limitations, the study helps raise awareness of the high prevalence and negative outcomes of cognitive impairment as a recognized public health burden. It is time for the nephrology community to respond by screening for cognitive impairment using simple instruments, and by using the screening results to contribute to treatment planning and survival prognostication in discussions with patients and families. Future studies are needed to identify causes and potential interventions to treat cognitive impairment in CKD and ESRD patients.

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