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Original Investigation

Clinical Predictors of Individual Cognitive Fluctuations in Patients Undergoing Hemodialysis

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Background: Cognitive impairment in hemodialysis (HD) patients is frequent and mediated by several factors. It is unclear which patients are more susceptible to cognitive variations around the dialysis cycle and which clinical factors may play a mediator role. We aimed to answer these issues by investigating intra-individual changes within the dialysis cycle.

Study Design: Cross-sectional observational study with repeated measures.

Setting & Participants: 47 HD patients and 40 controls without kidney disease, both without history of neurologic disease.

Predictors: Dialysis vintage, disease duration, vascular risk factors, comorbidity index score, intradialytic weight change, frequency of hypotensive episodes, and biochemical levels (hemoglobin, leukocytes, urea, creatinine, sodium, and potassium). Covariates included demographics (age, education, and sex).

Outcomes & Measurements: Significant individual deterioration in attention and executive functions (phasic and intrinsic alertness, Stroop test, and Trail Making Test) after dialysis, as measured by a regression-based reliable change method. Regression models were used to identify clinical predictors of individual cognitive decline after dialysis.

Results: After dialysis, patients primarily showed prolonged reaction times and psychomotor slowing. However, individual-based analyses revealed that fluctuations in attention and executive functions were present in only a minority of patients. Significant individual fluctuations on particular attention and executive tasks were associated moderately with intradialytic hypotensive episodes, as well as with psychoactive medication, and were predicted weakly by blood leukocyte count, sodium level, dialysis vintage, and volume.

Limitations: Small sample size; patient group younger and healthier than the overall HD population, limiting generalizability.

Conclusions: Only a minority of patients exhibit significant individual cognitive fluctuations, predominantly showing deterioration after dialysis in attention and executive functions. Susceptibility to such fluctuations was predicted in part by both HD-dependent and -independent factors.

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INDEX WORDS: Chronic kidney disease; cognition; hemodialysis; cognitive impairment; fluctuations; reliable change; variations in cognitive function; neuropsychological assessment; attention; psychomotor speed; executive function.

Cognitive impairment in patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) is frequent[1-6] and shows increasing prevalence rates.[1,5] The relationship between cognitive impairment and HD, although still poorly understood, is believed to be multifactorial, including several traditional risk factors for cognitive impairment, such as older age,[1] in addition to the extra burden of several factors primarily and secondarily associated with CKD, for example, anemia,[7] hyperparathyroidism,[8] and depression,[3] and a high prevalence of cerebrovascular disease.[2,9]

Recent studies have suggested that there are significant variations in cognitive function during the course of a dialysis session, questioning how hemodynamic instability and fluid shifts during dialysis

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themselves may affect cognitive function.[10-12] The majority of studies have established that cognitive performance of HD patients is at an optimal level at around 24 hours after the HD session, whereas during and immediately before or after HD, patients usually show considerable deficits in memory and executive functions.[10-12] Given the etiologic and clinical heterogeneity of the HD population, identifying which patients show such fluctuations and which clinical factors they may be associated with is of particular clinical importance. The latest recommendations propose the use of individual-based statistical models as a way to improve accuracy in measuring cognitive changes.[13,14] Additionally they allow the reduction of several obstacles inherent to repeated neuropsychological assessment, such as practice effects, regression to the mean, or weak measure reliability.[14]

In the present study, we aimed to further characterize cognitive fluctuations within the HD cycle by investigating changes at the individual level. With this individual-based approach, we aim to identify which patients are particularly vulnerable to such fluctuations, with a special interest in possible declines after HD, by exploring which clinical variables might be associated with significant individual fluctuations of cognitive function. Given previous evidence of HD patients having a characteristic fronto-subcortical impairment profile,[15] we also predicted that psychomotor speed and executive function tasks would be especially sensitive to cognitive fluctuations.

METHODS

Study Population

Patients were recruited from the dialysis unit of the Division of Nephrology of the Rheinisch-Westfaelische Technische Hochschule (RWTH) Aachen University Hospital and 3 dialysis outpatient centers in the Aachen region. Patients were eligible to participate if they were 18 years or older, had sufficient German language knowledge, and were able to consent. Exclusion criteria included history of neurologic disease, chronic psychiatric disease, severe auditory or visual disability, and current unstable acute medical condition. We also recruited healthy control participants from the community and staff of the RWTH Aachen University. Exclusion criteria for the healthy control group also included kidney and cardiovascular (CV) disease.

Study Design

The neuropsychological assessment battery was administered twice to all participants. Patients were assessed the day before and directly after an HD session, and controls were measured twice within 24 hours. If unable to be tested within this time frame (eg, due to acute intercurrent illness or an unscheduled medical procedure), patients were assessed at the next possible time (70% within 24 hours, 20% within 48 hours to 1 week; and 10%, >1 week apart). Assessment order of the HD group was contrabalanced: 22 patients were assessed first before the dialysis session, whereas 25 patients were assessed for the first time after the dialysis session. All participants were tested individually by the same investigator in a quiet room. The study was approved by the ethics committee of the Medical Faculty of RWTH Aachen University (EK 179/11). Written informed consent was given by all participants.

Neuropsychological Assessment

The neuropsychological assessment battery (see Table 1) was assembled to include all major cognitive domains—attention, memory, executive functions, visuospatial processing, and language—using standardized and commonly used tests in clinical and research settings. To avoid practice effects, alternate forms of the tests were used for most instruments (except when unavailable, see Table 1). The order of test administration was kept constant, but we contrabalanced which version of the tests was used to avoid testing bias. The Boston Naming Test[16] and Incomplete Letters subtask of the Visual Object and Space Perception (VOSP) battery[17] were administered only once for exclusion of primary language and visuospatial deficits, which could hinder performance

Table 1. Neuropsychological Assessment Protocol: Cognitive Tests by Cognitive Domain and Measurement Time-Point

Cognitive Domain With Neuropsychological Tests and Subtests	Before HD	After HD	Alternate Forms Used
Screening			
Montreal Cognitive Assessment (MoCA)[43,44]	X	X	X
Mini-Mental State Examination (MMSE)[45]	X	X	
Attention			
Test of Attentional Performance (TAP)[46], phasic and intrinsic alertness subtests	X	X	
Verbal memory			
Digit span forwards[47]	X	X	
California Verbal Learning Test (CVLT)[48], total learning, interference, immediate recall, delayed recall, and recognition	X	X	X
Nonverbal memory			
Medical College of Georgia Complex Figures (MCGCF),[49,50] immediate recall and delayed recall	X	X	X
Visuospatial functions			
Medical College of Georgia Complex Figures (MCGCF), figures drawing	X	X	X
Visual Object and Space Perception (VOSP) Battery,[17] incomplete letters subtest	X		
Language			
Boston Naming Test short-form CERAD-Plus[16]	X		
Executive functions			
Digit span backwards[47]	X	X	
Verbal fluency: phonemic and semantic[51]	X	X	X
Trail Making Test[52]	X	X	X
Stroop test[53]	X	X	X

Abbreviation: CERAD, Consortium to Establish a Registry for Alzheimer's Disease.