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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.

on more complex tasks. For additional descriptions of each of the cognitive tests included, please see Item S1 (provided as online supplementary material). We also administered the Hospital Anxiety and Depression Scale (HADS),[18] for identifying depression and anxiety symptoms, and the Epworth Sleepiness Scale (ESS),[19] to measure daytime sleepiness, only once at the first measurement time. Subjective fatigue level was evaluated through a 10-point scale (0 = no fatigue and 10 = worst imaginable fatigue) at both measurement times (adapted from the Brief Fatigue Inventory[20]).

Clinical Variables

Sociodemographic data (age, sex, and years of education), medical history, and current medications were obtained for all participants by self-report or clinical records. Comorbid conditions were quantified using the Charlson Comorbidity Index, which predicts 10-year mortality by weighing several comorbid conditions, either corrected for dialysis[21] or corrected for age in healthy controls.[22] The presence of CV risk factors—diabetes, hypertension, hypercholesterolemia, smoking, and body mass index—was recorded for all participants. For HD patients, CV risk factors were rated using the low Systematic Coronary Risk Evaluation (SCORE) risk charts.[23] Medication was listed for all participants, and neuroleptics, antidepressants, opioids, and antiparkinsonian agents were considered psychoactive medication.

Clinical data for patients also included the cause of CKD, HD vintage, intradialytic weight change, and number of hypotensive episodes during HD treatment, defined as systolic blood pressure $<$ 90 and/or diastolic blood pressure $<$ 50 mm Hg measured every 30 minutes and obtained from the HD session protocol and clinical records. Biochemical data available for HD patients included serum values for hematocrit, hemoglobin, leukocytes, platelets, C-reactive protein, glucose, sodium, potassium, urea, and creatinine from routine blood samples obtained at the beginning of the HD session.

Statistical Analysis

Independent-sample *t*, Mann-Whitney, or χ^2 tests were used to determine group differences in demographic and clinical variables, depending on the comparison and test assumptions. We calculated a linear mixed model with random effects for correlated data, with education and testing order as covariates, to determine interactions between measurement time point and group performance (HD patients vs controls) in each of the cognitive measures. The model's goodness of fit and normality of residuals were verified.

To assess individual change, and using the healthy control group data as reference, we used a standardized regression-based method[24,25] to predict the retest score of each patient in each cognitive measure from their scores at initial testing, controlling for error in measurement (test-retest reliability), practice effects, and regression to the mean (ie, extreme scores on initial assessment generally will be less extreme at retest). The use of individual-based statistical methods is known to be compromised when reliability of the instruments is low,[26] so we calculated reliability coefficients for each test. Given their low reliability ($r < 0.3$), we decided to exclude the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) from further individual-based statistical analyses. Calculated models were adjusted for demographic variables (age and/or education) if previously flagged as significant predictors in an exploratory standard least-square regression model. Significant comparisons (2-tailed *t* test) of the standardized discrepancy (ie, *z* score $\pm$ 1.645 with a 90% confidence interval), between individual observed and predicted scores were categorized as reliable deterioration or improvement.

Subsequently, exploratory least-square linear regression models, controlling for outliers, were used to evaluate the association between cognitive performance after dialysis and a priori–chosen variables. We included standardized individual change scores as the dependent variable and, based on the available literature, the following clinical variables as predictors: depression, dialysis vintage, intradialytic weight change, intradialytic hypotensive episodes, number of psychoactive medications, and serum values of sodium, potassium, hemoglobin, leukocytes, hematocrit, urea, and creatinine. We then ran stepwise linear regression analyses to determine the weight of each predictor previously identified as significant. All statistical analyses were performed using SPSS, version 20 (IBM), with α set at 0.05 as the statistical threshold for significance.

RESULTS

Demographic and Clinical Characteristics

After screening, 319 patients were not included (6% mother language not German, 0.3% aged $<$18 years, 30.7% unable to consent [due to dementia, altered state of consciousness, delirium, or third-party legal custody]) or were excluded (30% neurologic disease, 8% psychiatric disease, and 19% systemic disease or unstable medical condition), whereas 6% were not willing to participate. We included 47 patients undergoing HD and 40 healthy controls.

Demographic and clinical characteristics are listed in Table 2. There were no group differences regarding age or male-female ratio. Control participants were slightly more educated than HD patients, which we controlled for in subsequent analyses. As expected, HD patients had a higher frequency of CV risk factors—diabetes, hypertension, and hypercholesterolemia—but did not differ regarding body mass index. The most frequent causes of CKD were diabetic nephropathy and glomerulonephritis, which account for almost half the HD patients (see Table 3). The average Charlson Comorbidity Index score indicated moderate to high mortality risk in the HD group.[21] Average dialysis vintage was 57 months. There was a mean intradialytic weight change of 1.56 $\pm$ 1.37 (SD) kg. The average number of intradialytic hypotensive episodes was 1 $\pm$ 1.91 (range, 0-8). Measurement times of patients were on average 20.2 $\pm$ 6 hours before the dialysis session, which corresponded to an average of 24.6 $\pm$ 4 hours after the last session—the known optimal cognitive function timing—and 2.3 $\pm$ 1.9 hours after dialysis.

Group Differences and Treatment Effects in Cognition

Group differences showed that HD patients performed worse than healthy controls on most cognitive tasks (see Table S1), with the exception of primary language and visuospatial abilities and verbal memory recognition. HD patients and controls showed similar levels of fatigue and sleepiness. Patients presented higher scores only on the depression subscale of HADS. Considering the interactions between group and time, the linear mixed-model analyses suggest an effect of HD session on attention and executive function tasks. After the dialysis session,

Table 2. Demographic and General Clinical Characteristics of the HD Patients and Healthy Controls

	HD Patients (n = 47)	Healthy Controls (n = 40)	*P*
Age (y)	57.3 ± 14.4	57.6 ± 11.9	0.9
Female sex	48%	55%	0.6
Education (y)	12.1 ± 2.8	13.5 ± 2.4	0.04
CV risk factors			
Diabetes type 2	45%	5%	<0.001
Hypertension	83%	33%	<0.001
Hypercholesterolemia	32%	0%	<0.001
Smoking (pack-y)	0.0 ± 1	0.0 ± 0	0.04
BMI (kg/m^2)	26.3 ± 7.7	25 ± 3.7	0.9
CV risk: SCORE	3.1 ± 4.2	—	—
Charlson Comorbidity Index score	5.9 ± 9.7	1.6 ± 1.4	<0.001
Medication			
Antihypertensives	83%	33%	<0.001
Oral hypoglycemic agents	2%	0%	0.4
Insulin	32%	0%	<0.001
Thyroid drugs	30%	10%	0.02
Antipsychotics	11%	0%	0.04
Antidepressants	11%	0%	0.04
Anxiolytics	2%	0%	0.4
Analgesics	20%	3%	0.02
Levodopa	4%	0%	0.2
Glucocorticoids	19%	0%	<0.001
Psychoactive medication	49%	3%	<0.001

Note: Values for continuous variables, as mean ± standard deviation. Charlson Comorbidity Index score corrected for dialysis in HD patients or corrected for age in the controls.

Abbreviations: BMI, body mass index; CV, cardiovascular; HD, hemodialysis; SCORE, Systematic Coronary Risk Evaluation.

Table 3. CKD and Dialysis-Related Clinical Variables of the HD Patients

Clinical Variables	Before/After HD (n = 22)	After/Before HD (n = 25)
Primary cause of CKD		
Diabetic nephropathy	11%	15%
Glomerulonephritis and systemic diseases	6%	15%
Hypertensive nephropathy	6%	4%
Polycystic kidney disease	9%	6%
Other	11%	4%
Unknown	4%	9%
CKD-associated comorbid conditions		
Renal anemia	17%	28%
Secondary hyperparathyroidism	17%	26%
Renovascular hypertension	11%	15%
History of kidney transplantation	4%	8%
Dialysis vintage (mo)	24	48
Intradialytic weight change (kg)	−0.6	−1.8
No. of hypotensive episodes	1.4 ± 2.4	0.6 ± 1.3
Hematocrit	0.28 ± 0.12	0.36 ± 0.50
Hemoglobin (g/dL)	29.3 ± 12.9	11.4 ± 1.9
Platelets (g/L)	313 ± 291	228 ± 124
Leukocytes (g/L)	9.1 ± 4.2	7.6 ± 1.9
C-Reactive protein (mg/L)	19	11
Glucose (mg/dL)	144 ± 54.9	104 ± 10.8
Sodium (mEq/L)	139 ± 2.3	138 ± 2.9
Potassium (mEq/L)	4.7 ± 0.7	4.6 ± 0.7
SUN (mg/dL)	88.0 ± 41.5	74.8 ± 37.3
Creatinine (mg/dL)	6.3 ± 2.8	5.7 ± 1.4

Note: Values for continuous variables are given as mean ± standard deviation or median. Reference values are as follows: hematocrit, 0.41-0.5; hemoglobin, 13.7-17.5 g/dL; platelets, 150-400 g/L; leukocytes, 4.2-9.1 g/L; C-reactive protein, <3-5 mg/L; glucose, <100 mg/dL; sodium, 136-145 mEq/L; potassium, 3.6-5.5 mEq/L; SUN, 16.6-48.5 mg/dL; creatinine, 0.70-1.20 mg/dL. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; glucose in mg/dL to mmol/L, ×0.05551. None of the group comparisons was statistically significant. Other causes include chronic progression of acute kidney disease due to postoperative infections, reflux diseases, and analgesic medication.

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis; SUN, serum urea nitrogen.

patients showed slower reaction times in both phasic and intrinsic alertness tasks, whereas healthy controls were faster on the corresponding retest measurement time. A similar slowdown pattern after HD was found on 2 subtasks of the Stroop test, letter reading and interference; whereas the time patients needed for task completion was prolonged or remained stable, control participants were significantly faster at retest. HD patients were slower at completing the Trail Making Test, Form B, after dialysis, but healthy controls did not show a significant change in performance time. HD patients also showed a slight reduction on a measure of verbal working memory, the reverse digit span, whereas controls showed slight improvement in performance. We did not find a differential effect of the dialysis session on the other cognitive measures.

Intraindividual Changes

Regarding changes at the individual level, regression-based standardized scores showed that across all cognitive domains, most HD patients exhibited stable performance over the cycle (ie, z score ≥ -1.645 to ≤ 1.645), and the percentage of patients with significant improvement (ie, z score ≥ 1.645) was marginal. As also shown in Fig 1, cognitive tasks in which HD patients showed significant deterioration (ie, z score ≤ -1.645) after the dialysis session included mainly timed tasks associated with attention, psychomotor speed, and executive functions (phasic and intrinsic alertness, Stroop test, and Trail Making Test),

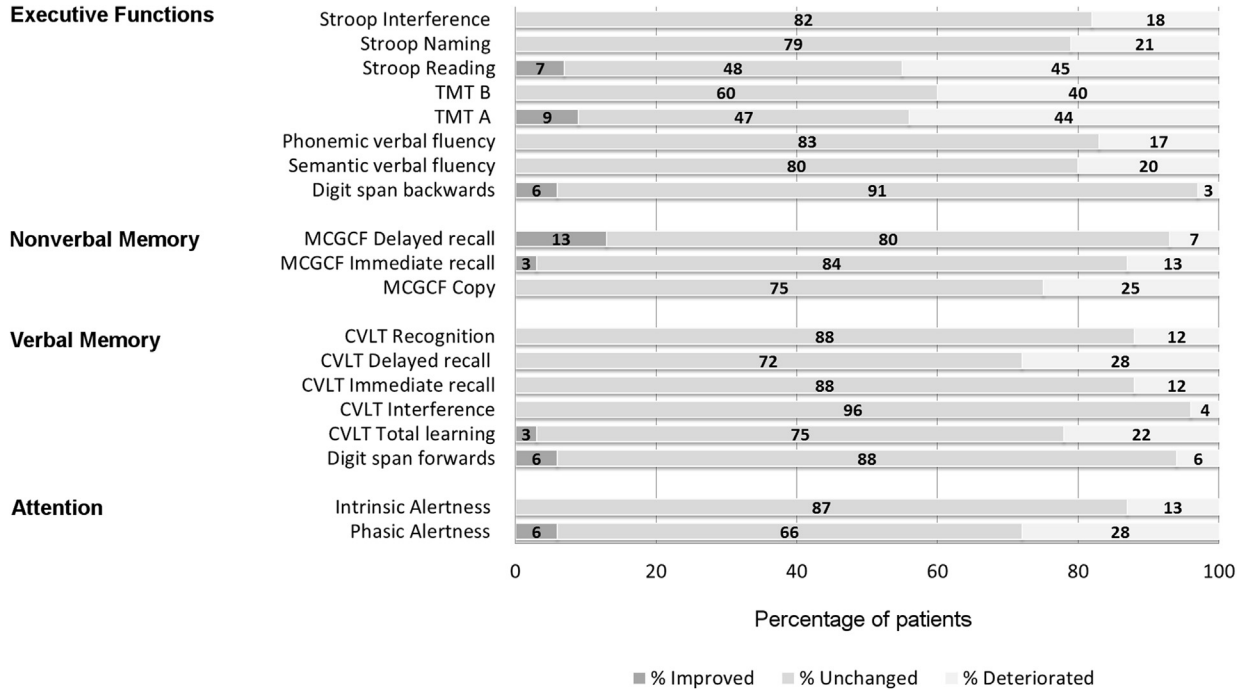

Figure 1. Percentage of hemodialysis patients showing significantly improved, unchanged, or deteriorated cognitive performance after the dialysis session compared to performance on a dialysis-free day, as calculated by a standardized regression-based method. Zero percentages not shown in labels. Most patients showed unchanged cognitive performance (z score ≥ -1.645 to ≤ 1.645) after a dialysis session compared to performance on a dialysis-free day. A minority of patients showed deterioration (z score ≤ -1.645) after dialysis; it was observed mainly in time-dependent tasks related to attention and executive functions. The percentage of patients presenting with significant improvement (z score ≥ 1.645) after dialysis was residual. Abbreviations: CVLT, California Verbal Learning Test; MCGCF, Medical College of Georgia Complex Figures; TMT, Trail Making Test.

but also verbal memory. Supplementary association analyses showed no significant effect of test-retest interval (30% of patients retested outside the 24-hour window) on significant individual fluctuations.

Predictors of Significant Cognitive Deterioration After Dialysis

We next analyzed to what degree clinical variables predicted the individual cognitive performance after dialysis (see tables *a-d* of Item S2 for complete results). Results show that an elevated frequency of intradialytic hypotensive episodes ($\beta = 0.46$; $P = 0.005$), higher number of psychoactive medications ($\beta = 0.93$; $P < 0.001$), and elevated predialytic blood leukocyte count ($\beta = 0.45$; $P = 0.001$) were associated with significant deterioration after dialysis in the intrinsic alertness task. The model, which explained 58% of the variance in performance, also included an association with lower depression scores ($\beta = -0.16$; $P = 0.03$), but this was a marginal predictor. Regarding performance in the phasic alertness task, worsening in performance after dialysis was predicted by an increased number of hypotensive episodes ($\beta = 0.26$; $P = 0.002$), higher blood leukocyte count ($\beta = 0.43$; $P = 0.001$), higher number of psychoactive medications ($\beta = 0.21$; $P = 0.005$), and dialysis vintage ($\beta = -0.01$; $P = 0.2$), albeit with a very marginal impact, with all predictors included in the model explaining 60% of variance in performance. Separate analyses show that the association with the frequency of intradialytic hypotensive episodes was not modulated significantly by other variables, such as pre- and post-dialysis blood pressure or presence of cardiac disease. Blood leukocyte count was associated positively with C-reactive protein level ($r = 0.42$; $P = 0.03$). Considering performance on the interference subtask of the Stroop test, 16% of the variance was explained in a model that predicted a significant change through a lower serum sodium level ($\beta = -0.12$; $P = 0.002$) and lower number of psychoactive medications ($\beta = -0.29$; $P = 0.007$). Lower intradialytic weight change ($\beta = -0.34$; $P = 0.03$) predicted worse performance in the Trail Making Test, Form A. The other regression analyses did not reach the established statistical significance threshold or no predictors were entered into the models.

DISCUSSION

Our study confirms that significant variation in cognitive performance may occur over the course of the dialysis cycle, but mainly demonstrates that only a minority of HD patients show significant intra-individual fluctuations. We additionally argue that when present, such fluctuations essentially depict

deterioration after the dialysis session and are confined primarily to neuropsychological tasks related to attention, psychomotor speed, and executive functions. Former studies may have overlooked this because they did not focus particularly on these cognitive functions. Moreover, in a more exploratory approach, we were able to show that individual fluctuations in such tasks were associated with several clinical variables; some were HD dependent, such as the frequency of intradialytic hypotensive episodes, but HD-independent factors such as psychoactive medication or current inflammatory status also yielded relevant clinical implications.

In general, HD patients performed worse than controls in most cognitive tasks, displaying a subcortical neuropsychological profile, similar to results of previous studies.[2,5,15,27] In accordance with earlier studies, after the dialysis session, HD patients tend to show a decline in cognitive performance[10,12] and/or no benefit of practice effects.[11,28]

However, our main objective was to better characterize cognitive fluctuations within the dialysis cycle by focusing on changes at the individual level. Results from the group and individual analysis methods may seem discrepant, but this is because the individual-based methods are more refined in the detection of change. Whereas group-based analyses provide only an estimate of the overall effect, over- or under-representing possible effects, individual-based methods are able to identify significant changes that occur in only a subset of participants.[26,29] Furthermore, use of individual-based analysis also has the advantage of controlling for several sources of measurement error inherent to repeated-measurements designs,[14] which group-based statistical analyses are not able to.

Therefore, we were able to reliably identify a significant decline after HD in a subset of patients, primarily confined to timed attention, psychomotor speed, and executive functions tasks. We believe these may be particularly sensitive to such fluctuations fundamentally due to 2 interconnected factors. Cognitive deficits in such tasks,[30] regardless of the time during the HD cycle,[31] are frequent in HD patients[30] and possibly are more prevalent than memory deficits in this population.[2,5] Furthermore, there is a plausible relationship between this type of subcortical cognitive impairment profile and the high prevalence of cerebrovascular disease in HD patients,[9,32,33] including silent brain infarcts, white matter hyperintensities, and microbleeds. White matter structural abnormalities may be particularly relevant because white matter integrity is believed to be important not only to variations in speed,[34] but also in association with cognitive performance variability.[35]

Focusing on both HD-dependent and -independent clinical variables, we identified some clinical variables that predict significant decline in attention and executive functions after HD, including an association between the frequency of intradialytic hypotensive episodes and performance in alertness measures after dialysis. Although available data were limited to simple frequency measurements, lacking information for duration and long-term history of hypotensive episodes, intradialytic hypotensive episodes are believed to cause damage to fronto-subcortical areas, given their increased sensitivity to cerebrovascular damage.[36,37] Additionally, there are reports of a significant association between hypotensive episodes and progression of frontal atrophy,[38] as well as between blood volume changes and cognitive impairment,[39] in HD patients, possibly due to changes in brain perfusion and metabolism.[40] Our results thus contribute to the available evidence of the importance of CV factors in the pathogenesis of cognitive impairment in HD,[33,41] extending its implications to the level of cognitive fluctuations in HD patients.

As expected from studies with healthy and diseased populations, including HD patients,[5] the association between psychoactive medication and cognitive impairment is not surprising, but had not been associated previously with significant fluctuations during the HD cycle. Although a more detailed analysis (eg, by active substance and dosage) was not possible, the intake of psychoactive medication predicted a significant individual decline in attention and executive performance after HD.

Although none of the patients fulfilled criteria for delirium, we also found an association between significant decline in alertness and blood leukocyte count. Given the C-reactive protein levels, this probably can be explained by inflammatory processes, including infection in some patients, which are known to be accompanied by possible diffuse cognitive dysfunction.[42] Another significant predictor of decline in attention performance was a high depression score. Depression generally is known to be associated with cognitive slowing, highly prevalent in the HD population, and an important mediator effect on cognition, namely processing speed and executive function.[3]

As discussed by Griva et al,[10] an association between neuropsychological performance and several modifiable CKD- and HD-related variables, including biochemical variables, may occur only when values go over or fall below a set threshold. This may explain why several studies did not find an association between cognitive fluctuations and clinical parameters. Because we applied an individual-based statistical model and the available values were collected before the HD session, we could expect some variation to exist, at

least in some patients. Thus, the association between sodium level, dialysis vintage, or intradialytic weight change and performance in attention and executive functions tasks, though plausible, was weak, and probably also mediated in part by other factors.[5] Therefore, a larger and more representative sample is needed to shed more light on these associations.

Because cognitive variability itself may be an indicator of increased vulnerability and risk of cerebral changes, one possible way to clarify the relationship between cognitive impairment, fluctuations, and brain injury may include the use of neuroimaging methods that allow identification of the structural and functional correlates of such variations.[28] Identification of mediating clinical variables is of equal clinical relevance for the detection and prevention of risk factors.

The present study has several strengths. First, we conducted a detailed neuropsychological assessment before and after dialysis, including several timed tasks of attention and executive functions that appear to be especially sensitive to cognitive impairment in HD. More importantly, using individual-based statistical methods, we were able to more reliably describe changes in relationship to the time point within the dialysis cycle. It is important to note that differences in the timing of the assessment within the HD cycle also may explain the differing results across studies.[10] In this respect, it is conceivable that greater cognitive fluctuations could be observed when assessing time points known to be associated with even worse cognitive performance, specifically just before or during the dialysis session[10,12] or at the end of a weekend without dialysis.[11,28] Furthermore, patients may not show such fluctuations within every HD session, potentially leading to underestimation in our present sample.

Other limitations include the representativeness of our small sample and generalizability of our findings. We studied predominantly young patients with fewer comorbid conditions than in the general HD population. Given this and because we collected only routinely available clinical data, we were not able to include other potentially relevant clinical variables, including nontraditional vascular risk factors, or offer a more detailed clinical characterization (eg, duration of hypotensive episodes). Response rates on cognitive testing also show discrepancies due to motivational issues and the associated complexity of some tasks.

In conclusion, recognizing the clinical heterogeneity of patients undergoing dialysis, we demonstrated that individual-based analyses may be helpful in identifying subtle subclinical fluctuations in cognition. Identifying their associated clinical parameters enhances our pathophysiologic understanding of cognitive impairment in these patients. Identification of patients who show significant fluctuations within the dialysis cycle is clinically relevant because such impairments have an impact on patients' daily lives and may hamper clinical communication. The association of these fluctuations with CV disease burden and non−dialysis-related factors (such as psychoactive medication) should encourage clinicians to identify patients particularly vulnerable to such acute fluctuations and optimize their treatment.

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SUPPLEMENTARY MATERIAL

Table S1: Neuropsychological assessment of HD patients and controls per measurement time-point.

Item S1: Description of the neuropsychology battery.

Item S2: Stepwise multiple regression tables for predictors of cognitive deterioration after HD.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.02.012) is available at www.ajkd.org

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