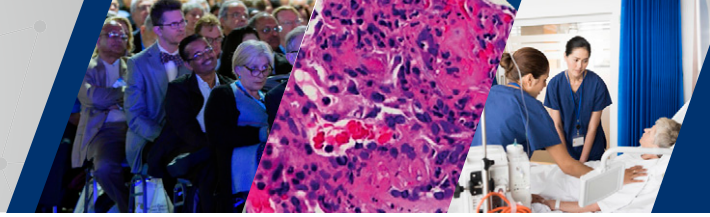

Cerebral Ischemia and Cognitive Dysfunction in Patients on Dialysis

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Case

A 69-year-old woman with a baseline creatinine of 3.1 mg/dl (eGFR of 16 ml/min per m^2) secondary to hypertension and vascular disease presents with retrosternal chest pain. Her previous history includes a previous myocardial infarction and cerebral vascular disease (stroke 1 year ago with residual right-sided weakness). A cardiac catheterization identifies residual disease in all vessels with a 70% stenosis in the right coronary artery and a drug eluting stent is inserted. After catheterization, the patient requires urgent dialysis for acute heart failure and AKI (creatinine 4.7 mg/dl, eGFR 7 ml/min per 1.73 m^2). The initial hemodialysis (HD) order was 2.5 hours, with a goal to remove 1.0–1.5 L of fluid. Her blood flow rate was 250 ml/min and a F600 dialyzer was used, with no anticoagulation. She remained hemodynamically stable after the first hour, with 1 L of fluid off and a 5 mm Hg decline in systolic BP. After 90 minutes, she became acutely confused, with worsening right-sided weakness, and the dialysis was stopped. The confusion and neurologic symptoms resolved within 2 hours postdialysis. Urgent blood work revealed no identified cause for the confusion.

Question 1. What is the primary cause for her confusion and worsening of her right-sided weakness?

A. Dialysis-associated disequilibrium syndrome from the initial dialysis
B. Thrombotic stroke resulting from the cardiac angiogram/angioplasty/stent insertion
C. Hemorrhagic stroke secondary to uremic platelets, and antiplatelet therapy
D. A decrease in perfusion to the cerebral ischemic area at risk because of the fluid removal by HD

Answer: D

A magnetic resonance imaging (MRI) scan of her head revealed an extended left perforator artery distribution infarct, cortical and subcortical involvements in the left occipital, and moderate to severe left internal carotid stenosis.

There is growing literature supporting the effect of HD-induced circulatory stress on end organs (1). Intradialytic circulatory stress can result in cardiac stunning and accelerated loss of residual kidney function. The brain and the kidneys have many common anatomic and vasoregulatory features: both are low-resistance end organs exposed to high-volume blood flow, increasing susceptibility to ischemic damage. Although cerebral autoregulation resists changes in cerebral blood flow, regulatory responses can be dysfunctional in patients on HD. Hypertension, atherosclerotic disease, and older age can also impair cerebral autoregulation. The combination of hemodynamic instability during HD and diminished cerebral autoregulation may lead to cerebral hypoperfusion and subsequent ischemic injury. Recent studies have shown that a transient decline in cerebral blood flow correlates with intradialytic cognitive dysfunction in patients undergoing HD (2–4). One study reports the acute effect of conventional HD on cerebral blood flow, measured by [^{15}O]H_2O positron emission tomography–computed tomography (PET-CT) (3). Global cerebral blood flow declined significantly over the course of a single HD session. Regional cerebral blood flow declined in the frontal, parietal, temporal, and occipital lobes, the cerebellum, and the thalamus. Higher tympanic temperature, ultrafiltration volume, ultrafiltration rate, and pH were significantly associated with a lower cerebral blood flow. A second study found similar results in a prospective, observational, cohort study of 97 adults, using transcranial Doppler ultrasound to measure cerebral arterial mean flow velocity throughout dialysis, with assessment of cognitive function during and off dialysis and after 12 months of treatment (2). Mean flow velocity declined significantly during dialysis, correlating with ultrafiltrate volumes and intradialytic decline in cognitive function, including verbal fluency and global and executive function. MRI white matter hyperintensities, a marker of small vessel disease, was also associated with these changes in cognition.

This patient has significant blockage in the left carotid stenosis, which likely contributed to a decline in blood flow and specifically to a decrease in perfusion to the cerebral territory at risk, contributing to the confusion and worsened right-side weakness. Cold dialysis has been shown to maintain perfusion during HD and may be an option.

Option A: Dialysis disequilibrium syndrome is a poorly defined constellation of symptoms, which

develops in patients receiving HD, usually during or immediately after the first HD treatment. Early symptoms include headache, nausea, disorientation, restlessness, and blurred vision; however, some patients may progress to confusion, seizures, coma, and even death. The symptoms of dialysis disequilibrium syndrome are caused by water movement into the brain, leading to cerebral edema (5). One theory proposed is reverse osmotic shift induced by urea removal. HD rapidly removes small solutes such as urea, particularly in patients who have marked azotemia. The reduction in urea lowers the plasma osmolality, thereby creating a transient osmotic gradient that promotes water movement into the cells. In the brain, this water shift produces cerebral edema and a variable degree of acute neurologic dysfunction. This patient's urea was not excessively high (40 mg/dl), her blood flow rate was low at 250 ml/min, and a low surface area dialyzer was used, making dialysis disequilibrium syndrome less likely.

Options B and C: Both of these options would need to be considered; however, it is less likely that the symptoms would resolve shortly after dialysis cessation. The MRI did not show any area of hemorrhage or new territory stroke.

Case Continued

Fortunately this patient did well after an initial session of dialysis. There was no further angina and kidney function returned to baseline, as did her cognitive and functional status.

In her CKD clinic follow-up, her creatinine level is back to her baseline of 3.1 mg/dl. The multidisciplinary team is meeting to discuss modality educational supports for this patient.

Question 2. What is the preferred next step in this patient's management for selecting options for kidney replacement therapy?

A. Wait 3–6 months after non ST elevation myocardial infarction and then refer to the surgeon for creation of an arteriovenous access
B. Refer to the peritoneal dialysis (PD) unit for assessment of PD suitability
C. Refer for a deceased donor transplant as there are no available living donors
D. Continue to follow without discussion of dialysis options

Answer: B

The key drivers to ischemia induced injury on HD have been the ultrafiltration volume/rate and relative hypotension. The hemodynamic response to PD appears to be more metabolic (glucose exposure, hyperinsulinemia, glucose degradation products) and volume effects (6). Most of the acute variations in systemic hemodynamics in PD occur during drainage and installation of dialysate from the abdomen. In a small study of patients with PD, left ventricular regional wall motion abnormalities occurred infrequently after a PD dialysate exchange (7). As described in the previous section, there is a growing body of evidence to support a decline in cerebral blood flow, contributing to cognitive decline during HD. However, little is known about cognitive changes in PD, particularly when comparing treatment modalities. A recent study compared 96 patients on HD and 101 patients on PD from the start of dialysis to 1 year, measuring executive function and attention (8). Although both groups revealed improvement over 1 year, PD was associated with improved cognitive outcomes compared with HD. A retrospective study found a higher incidence of dementia in those on HD compared with those in PD (9). A prospective study found that cognitive function declined faster with HD as compared with PD, despite similar baseline cognitive scores and adjustment for education and demographics (10). There are multiple limitations in all of these studies, including inability to control for all variables and limitations of the cognitive testing. However, cognitive function is of the utmost importance, influencing the patient's abilities to understand and process information, to participate in decision making, and to adhere to complex medical and dietary regimens. Understanding the effects of the dialysis modality is extremely important to patients when making their modality decisions. There is an urgent need for more research in this area.

This patient has a decrease in flow to the brain because of her poor vascular health and specifically the carotid stenosis. Kidney replacement with PD may be the preferred modality to preserve her brain health.

Option A: Conventional HD may not be the preferred modality for this patient because of the demand required to remove fluid in a limited period of time, provoking a decrease in perfusion to vital organs. If HD was the chosen dialysis method, a more frequent dialysis schedule or cooling the dialysate could be considered.

Option C: The deceased transplant list is dependent on blood type (5 years for type O and B and 2–3 years for AB and B in the United States). In Canada, the patient must have started dialysis to be on the deceased transplant list and she does not have an available donor. She also requires further risk stratification from a cardiac perspective and consideration of her other comorbidities.

Option D: This patient does require discussion and decision making regarding modality choices, particularly to align home therapy with her preferences and values. Consideration of PD does require assessment of the patient's functionality, their home environment, and their abdominal anatomy and physiology.

Acknowledgments

For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are one of the most exciting venues. The Nephrology Quiz and Questionnaire (NQ&Q) is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. The expert discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical areas of nephrology. These cases were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her case discussions, which serves as the main text of this article (Mark A. Perazella and Michael Choi, Comoderators).

Disclosures

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