CHAPTER 133

Effect of Extracorporeal Therapies on the Brain

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OBJECTIVES

This chapter will:

1. Describe the effect of hemodialysis and peritoneal dialysis on stroke and cognitive function.
2. Discuss dialysis adequacy, acute disturbances such as delirium, and dialysis disequilibrium syndrome in using of hemodialysis and peritoneal dialysis.
3. Review considerations in the use of continuous renal replacement therapy over intermittent hemodialysis in a patient with an acute brain injury.
4. Explore the practical aspects and concerns in using extracorporeal membrane oxygenation on the brain.

EFFECT OF HEMODIALYSIS AND PERITONEAL DIALYSIS ON THE BRAIN (CHRONIC SETTING)

End-stage renal disease (ESRD) is a major health burden worldwide and becomes increasingly common all over the world. In addition to kidney transplantation, hemodialysis (HD) and peritoneal dialysis (PD) represent two options for renal replacement therapy in patients with ESRD. Substantial cross-talk occurs between the kidney and the brain, as indicated by the frequent presentation of neurologic disorders, such as stroke, cognitive impairment, and neuropathy during the natural history of chronic kidney disease (CKD).[1] The advent of dialysis has led to a reduction in the rate of neurologic complications associated with uremia, but a new set of complications have arisen as a consequence of the effects of dialysis on the central nervous system over the short and long term.

HEMODIALYSIS AND PERITONEAL DIALYSIS ON STROKE

Stroke is a major health concern for maintenance hemodialysis (MHD) patients, with an incidence 8 to 10 times greater in these patients than that observed in the general population.[2,3] The mortality rate of stroke is approximately three times higher in patients on hemodialysis than in patients with CKD not undergoing hemodialysis.[4,5] Risk factors associated with stroke that are attributable to hemodialysis include hemodynamic instability, vascular access type, and risk of thromboembolism, amyloidosis, vascular calcification, and time spent on hemodialysis.[6,7] A study of 151 consecutive patients undergoing MHD patients who incurred an acute stroke found that 34% of ischemic strokes and 19% of hemorrhagic strokes occurred either during or within 30 minutes of concluding hemodialysis.[6] Data obtained from the US Renal Data System (USRDS) also showed that the incidence of stroke increased markedly during and immediately after hemodialysis, further suggesting that hemodialysis may increase the risk of stroke.[8] The removal of solutes and excess fluid during hemodialysis can result in low cerebral blood flow (CBF) and may predispose patients to ischemic stroke in the setting of flow-limiting vascular lesions.[6] The association between stroke and high interdialytic weight gain is not clear, but it seems reasonable to assume that low interdialytic weight gain would be associated with greater hemodynamic stability and a lower risk of stroke.

Patients undergoing peritoneal dialysis have a higher incidence of hospitalization resulting from ischemic and hemorrhagic stroke compared with age- and sex-matched controls.[9] However, patients undergoing peritoneal dialysis are less likely to suffer hemorrhagic stroke than those undergoing hemodialysis, possibly because of the use of anticoagulants during hemodialysis sessions.[9] Wang et al. showed that release of glutamate into extracellular tissues during acute stroke causes neuronal death because of its excitotoxic properties.[10] Peritoneal dialysis is effective in removing glutamate,[10] and experimental evidence from animal models indicates that removal of glutamate by peritoneal dialysis can reduce infarct size and restore functional brain tissue.[11]

HEMODIALYSIS AND PERITONEAL DIALYSIS ON COGNITIVE FUNCTION

Cognitive impairment in CKD increases the risk of mortality[6] and has major implications on the ability to provide informed consent to dialysis initiation and dialysis maintenance. Moderate to severe cognitive impairment occurs in 30% to 60% of patients undergoing hemodialysis,[12] and two thirds of patients undergoing peritoneal dialysis.[13] Cognitive impairment in patients considering dialysis initiation could affect their ability to complete an informed consent to agree to initiate treatment. Once initiated, cognitive impairment at this level adherence to treatment protocols, and have an adverse effect on costs, dialysis technician time, and number of hospitalizations.[14–16]

The pathophysiology of cognitive impairment in patients on dialysis may be mediated by three main routes: traditional risk factors, such as older age, sex, black ethnicity, diabetes mellitus, hypertension, low educational status, and cardiovascular disease;[14] nontraditional factors, including hyperparathyroidism, elevated FGF 23 levels,[17] low vitamin D levels,[18] anemia,[14] malnutrition, inflammation,[19] and oxidative stress; and dialysis-associated factors, such as adequacy,[20,21] dialysis modality,[22] hemodynamic instability during the procedure, and solute shifts.[23]

The majority of studies that have investigated cognitive function in patients on dialysis have focused on hemodialysis, but several studies have been performed in patients undergoing peritoneal dialysis.[13] The USRDS reported in 2005 that cognitive impairment rates for patients undergoing hemodialysis are 1.5 to 2.0 times higher than for those

undergoing peritoneal dialysis, with a strong age effect.[24] The mechanisms of cognitive impairment associated with peritoneal dialysis may be similar to those associated with hemodialysis, with the exception that hemodynamic instability and rapid changes in CBF are not seen in patients undergoing peritoneal dialysis.

A report in 2011 of a matched model using USRDS Medicare claims data also indicated that the risk of incident dementia for patients who started on peritoneal dialysis was lower than in those who initiated on hemodialysis.[25] A smaller study using primary data collection, however, found that cognitive impairment was almost as common in those undergoing peritoneal dialysis as in those undergoing hemodialysis.[13] The cohort undergoing peritoneal dialysis was, however, on average 11 years younger than those undergoing hemodialysis, and this finding therefore requires further investigation.[13]

DIALYSIS ADEQUACY AND COGNITIVE FUNCTION

Observational studies have reported an improvement in cognition after the completion of a dialysis session, suggesting a role of uremic toxins in cognitive dysfunction.[26] The Frequent Hemodialysis Network study, however, compared cognitive function in patients undergoing nocturnal hemodialysis six times per week to those undergoing nocturnal hemodialysis three times per week and found no association between renal clearance and improved cognitive function. Preliminary analyses in the same study suggested an improvement in memory and verbal fluency in those undergoing more frequent hemodialysis. A longitudinal study of 12 patients who transitioned from standard thrice-weekly dialysis to daily nocturnal dialysis also reported an improvement in cognitive outcomes after 6 months.[22] Future large samples and randomized controlled trials with extensive follow-up are awaited to confirm whether frequent hemodialysis could improve cognitive function.

A Kt/V value is used to quantify treatment adequacy in hemodialysis and peritoneal dialysis. (K represents the relative efficiency of the dialyzer in removing harmful solutes from the circulation; t, the duration of the treatment; and V, the volume of urea in the body.) The current target set by the US National Kidney Foundation is a $Kt/V \geq 1.2$ for hemodialysis and a $Kt/V \geq 1.7$ for peritoneal dialysis.[27] Although it has been hypothesized that more frequent hemodialysis and therefore a potentially higher Kt/V may result in reduced accumulation of uremic toxins in the blood, a $Kt/V > 1.2$ has been associated with severe cognitive impairment in patients undergoing conventional hemodialysis.[21]

Dialysis may contribute to cognitive impairment by inducing hemodynamic instability, fluid shifts, intravascular volume loss, cerebral ischemia, or cerebral edema.[28–32] Strict volume control may have beneficial effects on cognitive function in hemodialysis patients.[33] Daily dialysis may offer an alternative because it does not induce the changes in cerebral circulation typically seen in thrice-weekly dialysis when large amounts of fluid are removed over a short period of time.

DIALYSIS DISEQUILIBRIUM SYNDROME

Dialysis disequilibrium syndrome (DDS) is an acute condition that typically occurs toward the end of a dialysis session and subsides after several hours. This syndrome first was reported in 1962 and is an extreme consequence of dialysis-associated cognitive impairment.[34] Patients may experience headache, nausea, and confusion during or after dialysis, but changes in treatment regimes, particularly increases in the frequency of dialysis, have reduced the prevalence of this complication. Administration of mannitol can be used to reduce intracranial pressure and improves symptoms in approximately 80% to 90% of patients.[35]

Ronco et al.[36] showed the brain density by computerized tomographic scan fell significantly during and after hemodialysis, whereas a decrease in density was not observed in normal subjects or in patients on continuous peritoneal dialysis. This change in the densitometric values of brain tissue suggests that there is a postdialysis gain in cerebral water linked to the intermittent treatment. Two hypotheses have been raised to explain the mechanisms behind dialysis disequilibrium syndrome. The first hypothesis proposes that rapid removal of urea by dialysis leads to a blood–brain urea gradient, resulting in water influx into the brain.[37] The second hypothesis proposes that the production of idiogenic osmoles within glycine, glutamine, sorbitol, and inositol contribute to the development of cytotoxic edema when an osmotic gradient is developed during rapid dialysis.[38] The movement of water and urea across the plasma membrane is facilitated by aquaporin channels and urea transporters, including AQP1, AQP4, AQP9, and UT B1 that are expressed in the brain.[39] An increase in expression of aquaporin channels facilitates an influx of water into the brain by osmosis, and a reduction in UT B1 expression slows urea egress from the brain.[39]

ACUTE DEFECTS IN COGNITION

Acute disturbances in cognition, such as delirium, can develop during a dialysis session in patients with poorly controlled blood pressure, or as a result of hypoperfusion and metabolic derangements, especially hyponatremia.[23] Many studies have performed repeated measures of cognitive function at various times during the dialysis cycle to examine the acute effects of dialysis on cognition.[40–45] Data from such studies have, however, been inconsistent, showing improvement and worsening of cognitive function after dialysis, probably because of a wide range of eligibility criteria, timing, and type of cognitive measurements, and the use of acetate instead of bicarbonate in early studies.[40–45] Several studies have reported optimal cognitive function 24 hours after dialysis that worsens over time since the last dialysis session.[35,37–41] The development of dialysis technology that uses a succinate-based dialyzing solution can improve cognitive function in hemodialysis patients.[46]

A comparison of cognitive function in patients predialysis and 24 hours postdialysis found a significant improvement in measures of attention, verbal and visual memory, and psychomotor speed at 24 hours.[42] Another study performed in 2007 performed repeated measures of cognitive function using a 45-minute battery of cognitive tests in 28 patients undergoing hemodialysis. An acute, clinically relevant decline in global cognitive function during dialysis was identified, which only partially resolved an hour after dialysis.[28] A study using repeat measures of cognitive function an hour before and an hour after dialysis found no marked differences in cognitive function. This study may have suffered bias because of a learning effect that was detected between first and second Word List Learning tests and the Digit Symbol Substitution tests because of

the use of identical rather than alternating versions of the cognitive tests.[47]

Studies are needed to determine whether repetitive episodes of delirium induced by dialysis can deplete neurotransmitters and cognitive reserve, thus contributing to an increased risk of chronic cognitive impairment. Dysregulation of cholinergic neurotransmission has an important function in the development of cognitive impairment. One study, however, suggested that the cholinesterase inhibitor rivastigmine could not improve cognitive function in critically ill patients;[48] whether dialysis can remove neurotransmitters and improve cognitive function in patients with ESRD remains unclear.

EFFECT OF CONTINUOUS RENAL REPLACEMENT THERAPY ON THE BRAIN (ACUTE SETTING)

Since the introduction of continuous renal replacement therapy (CRRT) into clinical practice in the early 1980s, it has represented a major advance in management of critically ill patients with acute kidney injury (AKI).[49–51] As a method of providing continuous dialytic therapy to critically ill patients, the use of CRRT in ICU patients has grown in popularity over the years.[52–54] The theoretical advantages of CRRT over intermittent hemodialysis (IHD) are the slower fluid removal, resulting in more hemodynamic stability and better control of fluid balance; the slower control of solute concentration, avoiding the risk of systemic hypotension; large fluctuations, fluid shifts, and dramatic changes in intracranial pressure (ICP), including a reduced worsening of cerebral edema,[55] the great flexibility, and the ability to perform the treatment with relatively simple and user-friendly machines.

In the patient with acute brain injury (ABI), the management focuses on lowering ICP and, most importantly, optimizing cerebral perfusion pressure (CPP).[56] Early in the course of brain injury, there is marked cerebral edema, which can cause a secondary ischemic injury. Early recognition and treatment can lessen this injury and is the focus of early management of ABI. IHD may worsen neurologic status by compromising cerebral perfusion pressure. This may be the result of a decrease of mean arterial pressure, which was due to dialysis-induced hypotension or an increase of cerebral edema and intracranial pressure. Dialysis disequilibrium results from the rapid removal of solutes, resulting in intracellular fluid shifts. Small observational trials and case reports in patients with intracranial pressure monitoring indeed reported increases in intracranial pressure with IHD.[57,58] CRRT offers several advantages over IHD in the patient with ABI including slower but prolonged total solute removal, preserved hemodynamics, more gradual improvement in acid/base disorders, and decreased vasogenic edema.[59] Furthermore, Fletcher JJ et al. showed that CRRT may have beneficial effects in patients with refractory intracranial hypertension because of gentle removal of fluid, solutes, and inflammatory cytokines.[60] Using CT scans to measure brain density, Ronco et al.[61] showed an increase of brain water content after IHD, whereas no such changes were observed after CRRT. Abdo demonstrated that, after 12 hours of continuous venovenous hemodiafiltration, the brain hemodynamics, including right middle cerebral artery (MCA), mean flow velocity, and right MCA pulsatility index, were stable.[62]

Patients with cerebral edema or intracranial hypertension have decreased or absent autoregulation of cerebral blood flow. A decrease in systemic blood pressure, as may occur during renal replacement therapy (RRT), therefore leads to decreased CBF and to cerebral ischemia, which consequently leads to more edema.[63] Back to the early years of RRT, continuous arteriovenous hemofiltration has been proven to better maintain CBF in patients with acute cerebral edema compared with IHD.[64,65] These findings have been extrapolated to treatment recommendations for patients with other causes of cerebral edema and to newer modalities of CRRT such as continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis (CVVHD).[66,67] Another argument in favor of a low efficient CRRT is that this therapy seldom is complicated with acute and important tonicity changes of the systemic circulation. Because IHD is a very efficient RRT modality, these changes may occur after a session of hemodialysis. A decrease in serum osmolality subsequently leads to water uptake by the cells and to development of cellular edema.[68] Intracranial pressure therefore may increase after IHD. Furthermore, Mathew RO, et al. showed that careful application of CRRT, probably early in the course of illness to avoid intradialytic osmolar shifts and provide hemodynamic stability, will allow for unimpeded neurologic recovery.[69]

Therefore KDIGO suggest using CRRT, rather than IHD, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema.[70]

Under standard conditions, CRRT is less efficient at solute clearance than IHD, resulting in slower removal of uremic toxins, and it seems logical that this mode of therapy is less likely to cause DDS.[71] Nevertheless, Shamir Tuchman et al. have reported occurrence of DDS with CRRT.[72] They highlight several important findings providing insights into the pathogenesis of DDS. First, despite a slower rate of urea reduction during CRRT, DDS can develop if the decreases in BUN and serum osmolality are of sufficient magnitude to induce fluid shifts in the brain. Second, DDS can occur even when the reduction in blood urea nitrogen (BUN) is modest if there is another electrolyte (e.g., sodium) contributing to the hyperosmolar state. Third, DDS can occur in patients with severe AKI. This study showed that the magnitude and rate of urea or osmolality decrease play important roles in the occurrence of DDS. Furthermore, Osgood M et al.[73] provide the effect of CRRT on acute brain herniation in brain-injured patients. They described brain herniation in a patient on CRRT, which is extremely rare. The slow decline in serum sodium and BUN levels, which are typical for CRRT, suggests that another cause of brain edema, such as hypoxia or vasogenic edema, should be ruled out.

Irrespective of the cause of cerebral edema, the literature raises important questions about potentially modifiable factors to reduce brain edema and herniation, such as the dialysis rate, the dialysate sodium level, or the urea reduction ratio (URR), which may not be monitored routinely by nephrologists for brain-injured patients. However, these articles are all case report, good-quality evidence; specifically randomized, controlled clinical trials will be necessary to establish the efficacy of CRRT on the brain.

EFFECT OF EXTRACORPOREAL MEMBRANE OXYGENATION ON THE BRAIN

Extracorporeal membrane oxygenation (ECMO) is a temporary artificial extracorporeal support of respiratory and/or circulatory support for potentially reversible severe

heart or respiratory injury untreatable with conventional therapies.[74] Recently, because of the technical and management improvements, the use of ECMO has increased dramatically in the last few years. ECMO therapy has improved outcome significantly in the patient of refractory cardiopulmonary failure, especially in the newborn. The most important ECMO study, which came from the UK collaborative ECMO Trial Group, showed that the survival of newborns with severe respiratory failure was better in the ECMO group compared with conventional treatment.[75] In addition, ECMO was likely to be as cost-effective as other life-extending technologies.[76]

Although ECMO provides a lifesaving technology and increasing survival rates, the morbidity in patients treated with ECMO therapy is related primarily to neurologic alterations such as cerebral injury, adverse neurodevelopmental impact, intracranial hemorrhage (ICH), hemorrhagic and ischemic cerebral lesions, and not pulmonary findings.[77] Because the improving survival rate of patients on ECMO, and the catastrophic effect of neurologic injuries in such patients, the topic of neurologic damage in ECMO is of major concern. Infants who are treated with ECMO in the neonatal period are at increased risk for cerebral palsy (10%–20%), mental retardation (15%), hearing impairment (3%–21%), and learning/behavioral problems (50%).[77,78]

Martucci G et al.[79] presented a case series of six neurologic injuries that occurred during the ECMO performance or after the ECMO weaning in 1 year. In each case the neurologic complication had a dramatic effect ranging from brain death to prolonged ICU stay and long-term disability. Likewise, Liebeskind et al.[80] demonstrated that cerebral microbleeds (CMB) may be noted after ECMO in children. It is suggested that gaseous emboli in the extracorporeal circuit may cause asymptomatic lesions, distinct from ischemic and hemorrhagic findings. Although strict neurological monitoring and increasing routine use of MRI may find that go beyond gross detection of hemorrhagic or ischemic lesions to uncover mechanistic aspects of what happens to the brain on ECMO, neurological complications are still a potential risk. The treated children were found to be highly at risk for developmental problems, most prominently in the motor domain in a Dutch follow-up study after ECMO by Nijhuis-van der Sanden et al.[81]

The possible pathophysiologic risk factors may be related to the neurologic injury during ECMO, including ligation and cannulation of major vessels supplying the cerebral circulation resulting the changes in pulsatility of the CBF pattern, prolonged anticoagulation, and potential for thromboembolic phenomenon and inflammatory insults.[77] Hunter CJ et al.[82] showed the negative effects that ligation of the right common carotid artery resulted in temporary decrease in CBF to the right cerebral cortex. In addition to ligation and cannulation of the cerebral circulation, early study in newborn lambs demonstrated that the ECMO treatment disturbs the cerebral autoregulation significantly.[83] Therefore CBF may be at increased risk of systemic blood pressure changes. This could be a risk for ischemic complications because of hypoperfusion as well as for hemorrhagic complications resulting from hyperperfusion. Furthermore, it has been found that gestational age, postconceptional age, acidosis, sepsis, coagulopathy, and treatment with epinephrine are independent factors associated with ICH in neonates who were treated with ECMO by Hardart GE et al.[84]

The mechanism that permits hypothermia to improve neurologic outcome has not been clarified yet. The recent pilot study reported by An Massaro et al.[85] evaluating the safety and feasibility of hypothermia as a neuroprotective strategy during ECMO showed that the bleeding complications observed were not beyond what is encountered routinely during ECMO support. Hypothermia suppresses the cerebral metabolic rate and possibly can protect the brain by permitting prolongation of ischemia time. It also decreases the secretion of glutamate and the production of oxygen free radicals. Concurrently, hypothermia is effective in reducing intracranial pressure that may be elevated after resuscitation.[86]

CONCLUSION

Although the development of dialysis technology, neurologic complications such as stroke and cognitive impairment have arisen as a consequence of the effects of dialysis on the brain over the short and long term. Stroke is a major health concern for hemodialysis and peritoneal dialysis patients. Because of the use of anticoagulants during hemodialysis sessions, patients undergoing peritoneal dialysis are less likely to suffer a hemorrhagic stroke than those undergoing hemodialysis. It is well known that the cognitive function was improved after the completion of a dialysis session. However, dialysis may contribute to cognitive impairment or DDS by inducing hemodynamic instability, fluid shifts, intravascular volume loss, cerebral ischemia, or cerebral edema. On acute setting, the use of CRRT is increasing in critically ill patients with AKI. Because of the advantage of CRRT, including slower fluid and solute removal, hemodynamic stability, more gradual improvement in acid-base disorders, and decreased intracranial pressure, we suggested using CRRT, rather than IHD, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. Nevertheless, DDS has been reported to occur with CRRT. Good-quality evidence, specifically randomized controlled clinical trials, will be necessary to establish the efficacy of CRRT on the brain. Although ECMO provides a lifesaving technology and increases survival rates, the morbidity in patients treated with ECMO therapy is related primarily to neurologic alterations such as cerebral injury, adverse neurodevelopmental impact, ICH, and hemorrhagic and ischemic cerebral lesions. Research is needed not only to determine the efficacy of these novel therapies but also to identify those patients most likely to benefit from such treatment.

Key Points

1. Stroke is a major complication in patients undergoing hemodialysis and peritoneal dialysis; conventional ischemic risk factors, as well as dialysis, can contribute to the development of stroke.
2. Cognitive function was improved after hemodialysis or peritoneal dialysis. Nevertheless, dialysis may contribute to cognitive impairment or DDS.
3. The frequent hemodialysis may improve the cognitive function. However, this is still controversial: the better dialysis adequacy, the more cognitive function was improved.
4. Compared with IHD, CRRT had many advantages, including slower fluid and solute removal, hemodynamic stability, more gradual improvement in

acid-base disorders, and decreased intracranial pressure.

5. It was suggested using CRRT, rather than IHD, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema.
6. Nevertheless, because of the magnitude of urea or osmolality decrease, hypoxia, and severe AKI, DDS has been reported to occur with CRRT.
7. The morbidity in patients treated with ECMO therapy is related primarily to neurologic alterations such as cerebral injury, adverse neurodevelopmental impact, ICH, and hemorrhagic and ischemic cerebral lesions.

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Full references for this chapter can be found on www.expertconsult.com.

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