SECTION 21

Interaction of the Brain and the Kidney

CHAPTER 131

Treatment of Combined Acute Renal Failure and Cerebral Edema

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OBJECTIVES

This chapter will:

1. Present the basic pathophysiology of cerebral edema.
2. Give the characteristics of patients at risk for cerebral edema.
3. Describe the standard supportive management of cerebral edema.
4. Discuss the issues to consider when prescribing renal support for the patient with cerebral edema.

BASIC PATHOPHYSIOLOGY OF CEREBRAL EDEMA

In the normal, healthy adult, the skull acts as a rigid box, containing the brain (approximately 80% of the intracranial volume), with its vasculature (10%), and the cerebrospinal fluid (CSF) (10%). Because the skull is not compressible, the Monro-Kellie doctrine states that any increase in the volume of its contents will result in an increase in intracranial pressure (ICP), unless there is a compensatory reduction or displacement in the volume of the other components.

Intracranial volume can increase as a result of cerebral edema. Typically, cerebral edema is divided into cytotoxic and vasogenic edema.[1,2] Cytotoxic edema develops as a consequence of neuronal and astrocyte cell swelling with maintenance of the integrity of the blood-brain barrier. Because glial cells outnumber neurons by 20:1, edema is mainly because of astrocyte swelling. Cytotoxic edema usually is caused by increased sodium (Na^+) and potassium (K^+) permeability of the cell membrane, energy depletion followed by failure of the energy-dependent ion pumps, the sustained uptake of osmotically active solutes, or some combination of these. In vasogenic edema, on the other hand, the integrity of the blood-brain barrier, comprising the endothelium and adjoining astrocytes, is disrupted, resulting in a protein-rich exudate with increased interstitial edema. Other causes of cerebral edema include interstitial edema that occurs in cases of severe hydrocephalus, wherein the CSF penetrates the adjacent brain because of the high CSF pressure, and osmotic cerebral edema, which is typified by the syndrome of inappropriate secretion of antidiuretic hormone, with an osmotic imbalance between the cerebral tissue and plasma.

ICP also can increase in association with increased cerebral blood volume, which can be caused by prolonged epileptiform neuronal activity, loss of vasoregulation resulting from disease, or physiologic stimuli such as hypercarbia or pharmacologic cerebral vasodilators. Similarly, hydrocephalus and space-occupying lesions can result in raised ICP.

Initially, the increasing intracranial volume is compensated by the combination of compression of the ventricles, displacement of CSF from the cerebral to the spinal subarachnoid space, increased CSF reabsorption by the arachnoid villi, and compression of the cerebral vasculature. CSF is produced in the choroid plexuses, mainly by the hydrostatic pressure gradient, so the CSF production rate falls as a result of the reduced arterial inflow and increased cerebral tissue pressure.

Because of these compensatory mechanisms, there is only a relatively small increase in ICP with increasing cerebral edema. However, eventually the buffering systems fail to compensate for further volume expansion, and then the ICP increases rapidly. This is shown in Fig. 131.1. The ICP tracing shows not only a higher mean value but also the increasing pulse wave amplitude as the swollen brain becomes less compliant during systolic arterial inflow.

The rate of change of ICP with increasing intracranial volume depends on the cause of the cerebral edema. Slowly expanding mass lesions can be better compensated than rapidly evolving edema. Even so, the development of

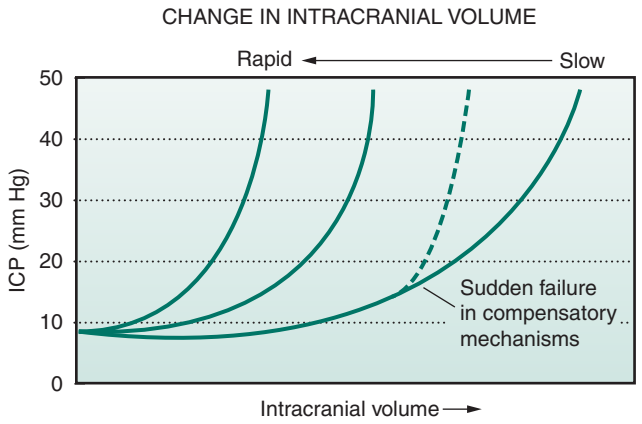

FIGURE 131.1 Relationship between intracranial pressure (ICP) and increasing intracranial volume. The change in ICP depends on the rapidity of the increase in intracranial volume. If the process is slow, then the compensatory mechanisms potentially can buffer changes more effectively than when there is a sudden increase in intracranial volume.

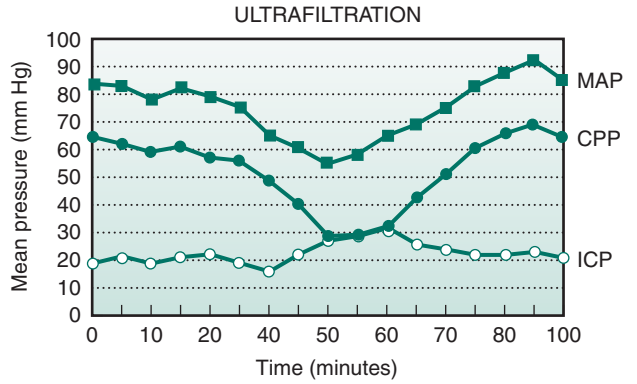

FIGURE 131.2 Changes in intracranial pressure (ICP), mean arterial pressure (MAP), and cerebral perfusion pressure (CPP). In this case, ultrafiltration initially led to a reduction in ICP and MAP, which then was followed by a rebound increase in ICP because of cerebral hypoperfusion.

hypoxia and/or hypercarbia can lead to a sudden increase in ICP in a patient with a slowly expanding mass. Similarly, acute falls in mean arterial pressure (MAP), which lead to a reduction in cerebral perfusion, can trigger reflex vasodilatation with increased vascular flow and a secondary increase in ICP (Fig. 131.2).

PATIENTS AT RISK OF CEREBRAL EDEMA

In addition to patients with known space-occupying lesions (including tumors and abscesses), traumatic head injury, extradural or subdural hemorrhage, or acute intracranial or subarachnoid hemorrhage and those who have undergone neurosurgery, many medical patients are at risk of cerebral edema. These include patients with endothelial damage resulting from vasculitis, such as the primary small vessel vasculitides, including systemic lupus erythematosus, microscopic polyangiitis, and secondary forms of vasculitis associated with infections such as leptospirosis. Cerebral ischemia ranges from small-vessel occlusion associated with cerebral malaria; to thrombosis seen with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or antiphospholipid syndrome; to larger-vessel ischemia including acute embolic and/or ischemic stroke. Infections, particularly those causing generalized encephalitis or severe bacterial meningitis, may be complicated by severe cerebral edema. Prolonged epileptic seizures also lead to cerebral edema.

Metabolic causes of cerebral edema in adults generally are restricted to acute and acute-on-chronic liver failure, although, rarely, cerebral edema has been reported in chronic liver disease. Occasionally, runners develop cerebral edema on a hot day because of substantial retention of ingested water and renal failure caused by rhabdomyolysis and heat exhaustion. Patients can develop cerebral ischemia and edema after solid organ transplantation associated with abrupt changes in plasma sodium concentration and also related to immunophilin toxicity. Other drugs that can cause cerebral edema include the monoclonal antilymphocyte agent OKT3, and valproate (encephalopathy resulting from hyperammonemia), and occasionally night clubbers taking 3,4-methylenedioxymethamphetamine (MDMA) (ecstasy) in combination with unrestricted water consumption as a result of cerebral water intoxication.

In children, inborn errors of metabolism, including those affecting the urea cycle, may predispose to cerebral edema during times of stress and supplemental feeding. Similarly, cerebral edema may occur during the treatment of diabetic ketoacidosis, particularly in young children, which is associated with a rapid fall in plasma glucose.[3] Acute kidney injury is not limited simply to the kidney; the inflammatory effect becomes systemic, as the kidney fails to effectively clear inflammatory cytokines and other mediators including damage-associated molecular patterns. The inflammatory response increases permeability of the blood-brain barrier, and the accumulation of azotemic toxins is controlled initially by brain astrocytes and pericytes, but once these homeostatic mechanisms have been overwhelmed, then changes in brain milieu develop, and as such the brain in patients with acute kidney injury is much more vulnerable to ischemic and other insults, including drug toxicity.[4,5]

SUPPORTIVE MANAGEMENT OF PATIENTS WITH CEREBRAL EDEMA

General Standard Care

Brain perfusion, or the cerebral perfusion pressure (CPP), depends on the difference between the mean arterial pressure (MAP), traditionally measured at the level of the carotid artery siphon, and the ICP. Under normal circumstances, brain perfusion is autoregulated, and cerebral blood flow is maintained above a lower limit of 50 mm Hg. Below that limit, further reduction in CPP may lead to reflex vasodilatation (see Fig. 131.2), with increased cerebral blood volume and consequent increased ICP, which results in a further fall in CPP. Increased ICP within the limits of the cranial cavity then can result in brain herniation and death. It has been suggested that a higher CPP, greater than 60 mm Hg, is required in patients with traumatic brain injury or hepatic encephalopathy to prevent further cerebral ischemia, although there are case reports of patients surviving with lower CPPs.

The key basic management strategy for a patient with cerebral edema is to maintain normal physiology (Table 131.1). Because hypoxia and hypercarbia exacerbate

TABLE 131.1

Standard Support for Patients Who Have or Are at Risk of Intracranial Hypertension

Standard Support	
Normoxia	PaO_2 >11 kPa (83 mm Hg)
Normocapnia	$PaCO_2$ 4.5–5 kPa (34–38 mm Hg)
Maintain CPP	≥60 mm Hg
Moderate hypothermia	32–35 °C
Actively Treat	
Precipitating factors	Seizures/pyrexia Hyperglycemia Electrolyte imbalances Hypo-/hyperosmolality
With Sustained ↑ ICP	
Hypertonic saline	Plasma Na 145–155 mmol/L (mEq/L)
Mannitol	200 mL 20% over 15–30 min
Anesthetic agents	Propofol/thiopentone
Hyperventilation	$PaCO_2$ 4.0 kPa (28 mm Hg)
	Surgical decompression

CPP, Cerebral perfusion pressure; *ICP,* intracranial pressure.

ICP, patients should maintain a PaO_2 of greater than 11 kPa (82.5 mm Hg), with a $PaCO_2$ of between 4.5 and 5 kPa (49.5 to 55 mm Hg). To achieve these levels, patients may require elective intubation and ventilation. In those with raised ICP on the steep part of the ICP/intracranial volume curve (see Fig. 131.1), a modest reduction in $PaCO_2$ can lead to a significant fall in ICP. However, overventilation, by reducing the $PaCO_2$ too far, can result in further reduction in cerebral blood flow with resultant cerebral ischemia and further increase in ICP.[6] Nevertheless, in an acute emergency when there are signs of herniation or a severe sustained surge in ICP, a short period of hyperventilation ($PaCO_2$ < 3.33 kPa or 25 mm Hg) can be used. Some centers have used jugular venous oxygen monitoring to determine optimal hyperventilation, aiming for a venous saturation greater than 65%, but this technique can be affected by the relative amount of extracerebral blood flow, light intensity, and movement artifacts.[7]

Similarly, patients should be fluid resuscitated adequately and given vasoactive agents to maintain a CPP higher than 60 mm Hg[8] or a MAP at 75 to 90 mm Hg if the ICP is not monitored. Traditionally, patients are nursed with 30 degrees head-upright tilt, because this helps to reduce the incidence of nosocomial pneumonia and causes a modest reduction in ICP. However, in those patients on the steep part of the ICP/intracranial volume curve, the associated reduction in MAP caused by sudden tilting of the patient may result in an acute reduction in CPP,[9] and a lower tilt of 15 to 20 degrees is more appropriate in patients who require pressors.

Potential exacerbating factors, such as epileptic seizures, pyrexia, sepsis, blood glucose abnormalities, and electrolyte (particularly hyponatremia) and osmolality abnormalities should be identified and treated appropriately.[10]

Specific Medical Treatments for Intracranial Hypertension and Cerebral Edema

Steroids, which are effective in reducing peritumoral edema by regulating astrocyte aquaporin four-channel expression, have no role in traumatic cerebral injury or metabolic edema. However, early steroid administration has been shown to improve the outcome in childhood acute bacterial meningitis, although meta-analysis failed to show any advantage in cerebral malaria.[10]

Mannitol superseded urea therapy for the treatment of raised ICP in the 1950s. Initially, mannitol expands the intravascular compartment, by drawing water out of the tissues, and similarly reduces red cell volume. In hypovolemic patients, this can result in hypotension. The initial effect of mannitol on blood rheology causes reduced cerebrovascular resistance with increased cerebral blood flow and consequent autoregulatory deceased cerebral blood volume and ICP. After 30 minutes, the osmotic gradient that develops between the plasma and the brain then may lead to a further reduction in brain volume and ICP. Traditionally, mannitol is infused at a dose of 0.5 to 1.5 g/kg over 15 to 30 minutes,[11] and this is repeated provided that the plasma osmolality remains at 325 mOsm/L or lower. Mannitol therapy subsequently then may cause an increase in ICP. The reason for this is not well established but may be related to mannitol accumulation within brain tissue, with a resultant oncotic pressure gradient causing water to move back into the brain. In patients with acute renal failure, the baseline plasma osmolality is increased because of the raised urea concentration. The plasma osmolality should be monitored carefully before repeated boluses, because accumulating plasma mannitol may predispose to cerebral accumulation.

More recently, there has been increased use of osmotherapy with hypertonic saline for treating cerebral edema associated with head trauma and acute liver failure. Typically, 30% hypertonic saline is infused to maintain plasma sodium concentrations between 145 and 155 mmol/L (mEq/L), or it is given as a 20-mL bolus.[12] Other centers have used a 75-mL bolus of 10% hypertonic saline. Hypertonic saline is thought to work in a similar fashion to mannitol, with initial plasma volume expansion and increased cardiac output, caused by either increased preload or a possible additional inotropic effect, followed by a subsequent osmotic effect. The increase in plasma osmolality leads to water movement from the normal brain, which allows expansion of the damaged area of the brain. However, hypertonic saline has additional effects by inhibition of Na+-K+-2Cl-cotransporter-1 (NKCC1) and Na/H exchanger and also reducing aquaporin 4 (AQP4) channels in astrocytes, so reducing water and electrolyte movement from plasma into the brain. Hypertonic therapy has been reported to be successful in patients with acute renal failure.[4,5] As with mannitol, later complications have included subsequent increased or "rebound" intracranial hypertension, because sodium will move from the plasma water into the area of damaged brain and therefore increase water movement into the area of damage. In addition, many patients with cerebral edema have a degree of hyponatremia, and too rapid an increase in plasma sodium has been observed to cause seizures and central pontine myelinosis. The sodium and chloride load also may result in congestive heart failure or chloremic acidosis, so volume replacement has to be monitored carefully in the patient with acute renal impairment.

To reduce the risk of fluid overload, newer solutions containing a mixture of 7.5% saline in combination with 6% dextran have been developed; in early trials, these have been reported to be more effective than equimolar mannitol in reducing ICP.[12]

Physiotherapy and patient movement can result in increased ICP. Patients therefore should be nursed in a quiet environment if possible. Thiopentone is used to control status epilepticus and therefore was tried to control ICP on the basis of reducing neuronal metabolism and cerebral

blood volume. Initial studies showed promise in controlling ICP,[13] but thiopentone boluses often were complicated by hypotension. Similarly, propofol also was used as continuous infusion and bolus to control ICP, but, as with thiopentone, boluses also could reduce MAP. What has not been established is whether patients treated with thiopentone and/or propofol infusion are more susceptible to hypotension resulting from the administration of other drugs, such as alfentanil, or hypotension during renal replacement therapy. However, these drugs, particularly propofol, may provide additional benefits over other sedatives, such as midazolam, by reducing cerebral oxygen requirements.

More rarely, children treated by propofol infusion developed a severe metabolic acidosis. The majority of units in the United Kingdom currently use benzodiazepine sedatives such as midazolam and opiate analgesics such as fentanyl, both of which accumulate in renal failure.

Moderate controlled hypothermia in patients with acute liver failure has been reported to result in short-term beneficial effects, including an increase in MAP and CPP, associated with a reduction in arterial ammonia, brain metabolism, cerebral blood flow, brain cytokine production, and markers of oxidative stress.[14] However, randomized, multicenter, controlled trials in neurosurgical trauma have not shown an overall survival benefit of cooling patients to 33°C,[7] possibly because of the time taken to cool patients and the increased complications in the hypothermic group (e.g., pneumonia). In subsequent trials, moderate hypothermia proved superior to barbiturate coma in treating patients with raised ICP, and cooling to 35°C resulted in better indices of cerebral metabolism with least side effects of hypothermia for both patients with hepatic coma,[15] and neurological trauma.[16] Similarly, in acute liver failure additional cooling failed to demonstrate any advantages over modest cooling to 36°C.[17]

CHOOSING RENAL SUPPORT FOR THE PATIENT WITH CEREBRAL EDEMA

The key issue when deciding on the choice of renal support for the patient with cerebral edema is the CPP and the cardiovascular stability of the patient. The ideal treatment would have no adverse effect on the CPP or cerebral blood flow (Table 131.2). Secondly, too rapid a fall in plasma osmolality could lead to a further increase in ICP.

Several studies have reported that middle cerebral arterial flow velocity is reduced after standard intermittent hemodialysis[18] in stable, healthy, chronic dialysis patients without neurologic disease. Similarly, changes in cerebral blood flow in response to carbon dioxide were observed to be maintained, although this response has been shown to be reduced in anemic patients undergoing chronic dialysis.[17] However, intermittent hemodialysis was noted to reduce stroke volume and cardiac output by 20%, even though there was no significant change in blood pressure.[19] Advances in neuroimaging have shown that these changes in cerebral blood supply cause localized areas of cerebral ischemia, particularly in areas of dense white matter with reduced vascular supply.[19] In critically ill patients, intradialytic hypotension is more common,[20] with a corresponding decrease in CPP.[21] This typically accounts for the initial increase in ICP observed during intermittent hemodialysis and/or hemofiltration.[22] Until the advent of continuous hemofiltration and/or dialysis, peritoneal dialysis was the main alternative to intermittent hemodialysis for renal replacement, and it caused much fewer adverse changes in ICP and CPP. However, peritoneal dialysis can result in increased ICP and reduced CPP in compromised patients[23] because of changes in cardiac output and blood pressure associated with standard 2-L exchanges using higher glucose solutions.[23] Therefore continuous renal replacement modalities have become the standard therapy for treatment of cerebral edema.[24,25]

PRESCRIBING RENAL SUPPORT FOR PATIENTS WITH CEREBRAL EDEMA

Modality

Several studies demonstrated that standard intermittent hemodialysis treatments, using low-flux dialyzers, with dialysate warmed to 37°C.[26–28] As such, if intermittent hemodialysis is to be performed, then it preferably should be daily, and therapy time should be prolonged to minimize cardiovascular instability by reducing the ultrafiltration rate. Dialysis machines with relative blood volume monitoring and ultrafiltration feedback control are preferred. A high dialysate sodium concentration is required to improve cardiovascular stability and reduce the fall in plasma osmolality resulting from the rapid fall in serum urea. Dialysate temperature should be cooled to 35°C or set to isothermic, again, to improve cardiovascular stability during treatment. With daily treatment with extended time, dialysate

TABLE 131.2

Advantages and Disadvantages of Currently Used Renal Replacement Modalities

TECHNIQUE	ADVANTAGE	DISADVANTAGE
CRRT	Minimizes changes in intravascular volume Slow rate of change in plasma osmolality Cooling	Risk of hemorrhage if systemic anticoagulants are used with ICP monitors
Peritoneal dialysis	Slow rate of change in plasma osmolality Cooling No anticoagulation	Hyponatremic dialysates Hypertonic exchanges may result in reduction in CPP
Intermittent hemodialysis	No anticoagulation	Risk of reduction in CPP with rise in ICP Risk of dialysis dysequilibrium
Slow extended daily dialysis (hybrid dialysis)	Potentially anticoagulant free Possible reduced chance of nosocomial infection Cooling	Depending on duration of therapy, may not be as cardiovascularly stable as CRRT

CPP, Cerebral perfusion pressure; *CRRT,* continuous renal replacement therapy; *ICP,* intracranial pressure.

flow rates can be slowed to reduce the rate of fall in plasma osmolality; similarly, bicarbonate concentration can be reduced to 28 to 30 mmol/L (mEq/L) to prevent too rapid a correction of plasma bicarbonate.[25] Compared with standard routine intermittent hemodialysis, dialyzers with larger surface area and fast blood pump speeds are not required, and smaller dialyzers with lower blood flow rates should be chosen, designed to reduce the speed at which serum urea and osmolality fall during dialysis. Potential hypotensive reactions at the initiation of treatment caused by bradykinin production may be reduced by choice of membrane composition and by priming with isotonic sodium bicarbonate rather than normal saline.

These precautions for intermittent hemodialysis also apply to hybrid techniques of extended daily dialysis. For continuous renal replacement modalities, hyponatremic replacement solutions and dialysates should be avoided, and warming should be minimized to deliberately cool the patient. Sodium balance is maintained better with hemofiltration than with dialysis mode, because the sodium sieving coefficient is less than 1.0.

CT and other scanning showed fewer changes in brain water content with peritoneal dialysis than intermittent hemodialysis treatments.[27–28] However, in critically ill patients sudden changes in intraperitoneal pressure may affect the inferior vena cava and potentially reduce right atrial filling and cardiac output, so reducing CPP.[29] If peritoneal dialysis is chosen, then choosing a cycling machine with either small volume exchanges or a tidal prescription will help reduce abrupt changes in intraperitoneal volume and have less of an effect on cardiac output. Peritoneal dialysis fluids are relatively hyponatremic, and patients may require additional hypertonic sodium infusions to maintain a high plasma sodium concentration.

Anticoagulation

There is an increased risk of local bleeding around the site of ICP monitoring devices (risk greatest for intraventricular drain > subdural catheter > extradural monitor).[30] Therefore patients preferably should receive no anticoagulation, or only a regional anticoagulant such as citrate, nafamostat, or prostanoids. The potent vasodilatory prostanoids, prostacyclin and epoprostenol, may provoke an increase in ICP by causing hypotension.[31]

CONCLUSION

Patients who develop acute renal failure with cerebral edema should receive standard supportive medical care designed to augment cerebral perfusion and maintain CPP. These patients require adequate fluid resuscitation, and pressors may be necessary to support MAP. Sepsis should be sought actively and treated appropriately, as should electrolyte imbalances, and patients should be rendered euglycemic. Cerebral perfusion can be improved by the use of hypertonic saline and by maintaining an increased plasma sodium concentration. In addition, boluses of mannitol may have an additive effect. Cerebral volume can be reduced by controlled hyperventilation, although excessive hyperventilation may result in a reduction in cerebral blood flow. Mild hypothermia also may help to reduce ICP and cerebral metabolic demand. Sedative anesthetic agents reduce ICP, but bolus thiopentone and propofol also cause vasodilatation and may result in hypotension, limiting their effectiveness.

Preferably, renal replacement therapy should have a minimal impact on cerebral perfusion and CPP, because a reduction in either can result in a further increase in ICP. Therefore continuous modalities are preferred, because they allow the least changes in intravascular volume and have slower rates of change in plasma osmolality. If intermittent techniques are to be used, then treatment times should be extended, with reduced blood and dialysate flows, similar to slow extended daily dialysis/hemofiltration.

Key Points

1. The astrocyte is designed to maintain cerebral homeostasis and initially responds to osmotic stresses by changing intracellular electrolyte and water content.
2. Transcellular water transport through aquaporin channels is faster than urea transport through urea transporters.
3. Cerebral ischemia results in cerebral edema with a corresponding increase in intracranial pressure.
4. During renal replacement therapy, cerebral edema can occur because of osmotic changes—too rapid a reduction in urea and other plasma osmolytes—and also secondary to intradialytic hypotension.
5. Renal replacement therapy in patients at risk of cerebral edema/ischemia should be designed to minimize hypotensive episodes by using cooled high-sodium dialysates coupled with slower blood and dialysate flows.

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