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ORIGINAL ARTICLE

Rapid Unexpected Brain Herniation in Association with Renal Replacement Therapy in Acute Brain Injury: Caution in the Neurocritical Care Unit

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Abstract
Introduction We aim to raise awareness for the potential for rapid brain edema and herniation in acutely brain-injured patients undergoing renal replacement therapy (RRT), including one case undergoing continuous veno-venous hemofiltration. Dialysis disequilibrium syndrome (DDS) may have been a possible cause for the brain edema.
Methods We retrospectively reviewed four consecutive neurocritically ill patients in acute renal failure undergoing RRT between 2011 and 2013. Imaging, blood pressure, and laboratory data pre-, during, and post-RRT are presented in graphical form. We performed an extensive literature review.
Results All patients suffered rapidly progressive herniation and death from global brain edema closely related in time to RRT, without other identifiable causes even after detailed review by three neurointensivists. Common clinical symptoms included sudden onset fixed and dilated pupils with apnea, consistent with brain stem compression. Herniation was not reversed by high-dose osmotherapy, and all patients died. Our detailed literature review provides plausible mechanisms for DDS as the most likely cause for our patients' brain edema.
Conclusions Even today, sudden brain edema and herniation may occur in association with RRT in neurocritically ill patients. We call for the establishment of RRT guidelines in patients with acute neurological injuries.

Keywords Brain edema · Brain herniation · Renal replacement therapy · Hemodialysis · Dialysis disequilibrium syndrome · CVVH · Neurocritical care

Introduction

Global brain edema occurs with volume expansion due to an increase in brain water content, both interstitially and intracellularly [1]. As intracranial pressure rapidly rises inside the skull, edema-related mass effect leads to the compression of vital areas of the brain and ultimately to the interruption of blood flow to these areas ("brain herniation"). Consequences include irreversible loss of brainstem reflexes, apnea, and death. Renal replacement therapy (RRT), in particular intermittent RRT (IRRT) leads to osmotic shifts, which can create osmotic gradients in the brain. In rare cases, dialysis disequilibrium syndrome (DDS) may result [2]. Encephalopathy and headache are the most common symptoms, although rapidly progressive brain edema and death have also been described [1–5]. Hemodynamic fluctuations may also occur during RRT [6, 7], which, in the setting of impaired autoregulation due to

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acute traumatic brain injury (TBI), may intermittently decrease cerebral perfusion and further contribute to brain edema [6, 8]. Given the paucity of contemporary reports on DDS, brain edema with RRT after acute neurological injury, and the assumption that this complication may have been nearly eliminated by current RRT methods [9, 10], clinicians may not suspect DDS in the differential diagnosis of rapidly progressive brain edema. In addition, brain edema has not been reported with continuous RRT methods, such as continuous veno-venous hemofiltration (CVVH), which are increasingly used in critically ill patients who cannot tolerate IRRT and are recommended by experts for neurologically injured comatose patients [10].

We report a contemporary series of four cases of rapidly progressive brain edema with fatal herniation in neurocritically ill patients undergoing RRT, including CVVH. We hypothesize that DDS was a possible cause for their rapid fatal brain edema. We aim to raise awareness of the potential for rapidly progressive brain edema in this patient population, even with current IRRT and continuous RRT methods.

Materials and Methods

We performed a retrospective chart review of four consecutive patients with various acute neurological injuries; three admitted to the neurological intensive care unit at the University of Massachusetts Medical Center University Campus (UMMC) and one to an affiliated teaching hospital, between June 2011 and January 2013. The UMMC cases had known acute brain injury, while the fourth patient was pharmacologically paralyzed to facilitate ventilator synchrony and was not suspected to have neurological problems until clinical brain herniation occurred and brain imaging confirmed a large ischemic stroke. Head computed tomograms (HCT) and laboratory data were extracted from the electronic medical records. We paid particular attention to blood urea nitrogen (BUN) and urea reduction ratio (URR), as prior studies have implicated these measures in the development of osmotic gradients and DDS [11]. We recorded serum sodium (sNa) and bicarbonate because they affect osmolarity and their rapid changes may lead to brain edema. Systolic blood pressure (SBP) values were recorded hourly, as brain hypoperfusion may lead to hypoxic–ischemic injury and global brain edema. All cases were retrospectively and independently reviewed in detail by three board-certified neurointensivists (R.C., W.H., and S.M.) to investigate possible other causes for the herniation. In all cases, osmotherapy included intra-venous bolus administration of mannitol (1 g/kg) and 30 mL of 23.4 % hypertonic saline every 6 h in alternating fashion. Our Institutional Review Board was informed about this study in writing, and waived the need for full review and informed consent. Cases are presented in chronological order.

Case 1

A 17-year-old man presented with a traumatic brain injury after an unhelmeted skateboard accident with a Glasgow Coma Scale [12] of 5 and bilateral frontal contusions with traumatic subarachnoid and subdural hemorrhages on HCT. A hemicraniectomy was performed approximately 36 h after trauma for refractory intracranial pressure (ICP) elevation to 60 mmHg unresponsive to osmotherapy, hypothermia (34 °C), and pentobarbital coma. Post-operatively, ICP normalized to <10 mmHg, and he was slowly weaned off therapies for ICP control by hospital day 5. CVVH was initiated on hospital day 8 for acute renal failure from rhabdomyolysis present since admission (peak creatinine kinase 45,000 U/L). Due to persistent hyperkalemia (7.3 mmol/L), he was transitioned to IRRT after 3.5 h. Within 15 min of the completion of this first IRRT session, the patient developed 6-mm fixed pupils and loss of corneal reflexes. Osmotherapy with both agents was immediately administered. Pupillary reactivity (4 mm, reactive) was briefly observed (<1 h), followed by a return to the fixed and dilated state. HCT 1 h after IRRT showed diffuse loss of gray–white matter differentiation with global edema, and brain stem herniation (Fig. 1). Notably, the BUN decreased from 51 to 28 mg/dL, and his sNA from 172 to 162 mmol/L during a single IRRT session (Fig. 2).

Case 2

A 45-year-old man with stage 3 chronic kidney disease (baseline serum creatinine [sCreat] 1.8 mg/dL) presented with a left hypertensive basal ganglia hemorrhage. The patient was started on osmotherapy on hospital day 4 but required surgical clot evacuation on hospital day 8 for right uncal herniation. Osmotherapy was weaned over several days, and the patient had intact brain stem reflexes, symmetric pupillary reactivity, and purposeful left-sided movements. The patient was weaned from the ventilator after tracheostomy and only on trach mask with 40 % oxygen. His acute on chronic renal failure progressed (sCreat 7.7 mg/dl; BUN 165 mg/dl), requiring institution of IRRT on hospital day 18. The patient had four uneventful IRRT treatments several days apart. Because he had tolerated these well, the fifth treatment was aimed to more "aggressively" reduce his BUN, which remained elevated at 141 mg/dL. During this fifth IRRT, he suddenly became bradycardic and apneic with the loss of motor responses but preservation of pupillary, corneal, and cough

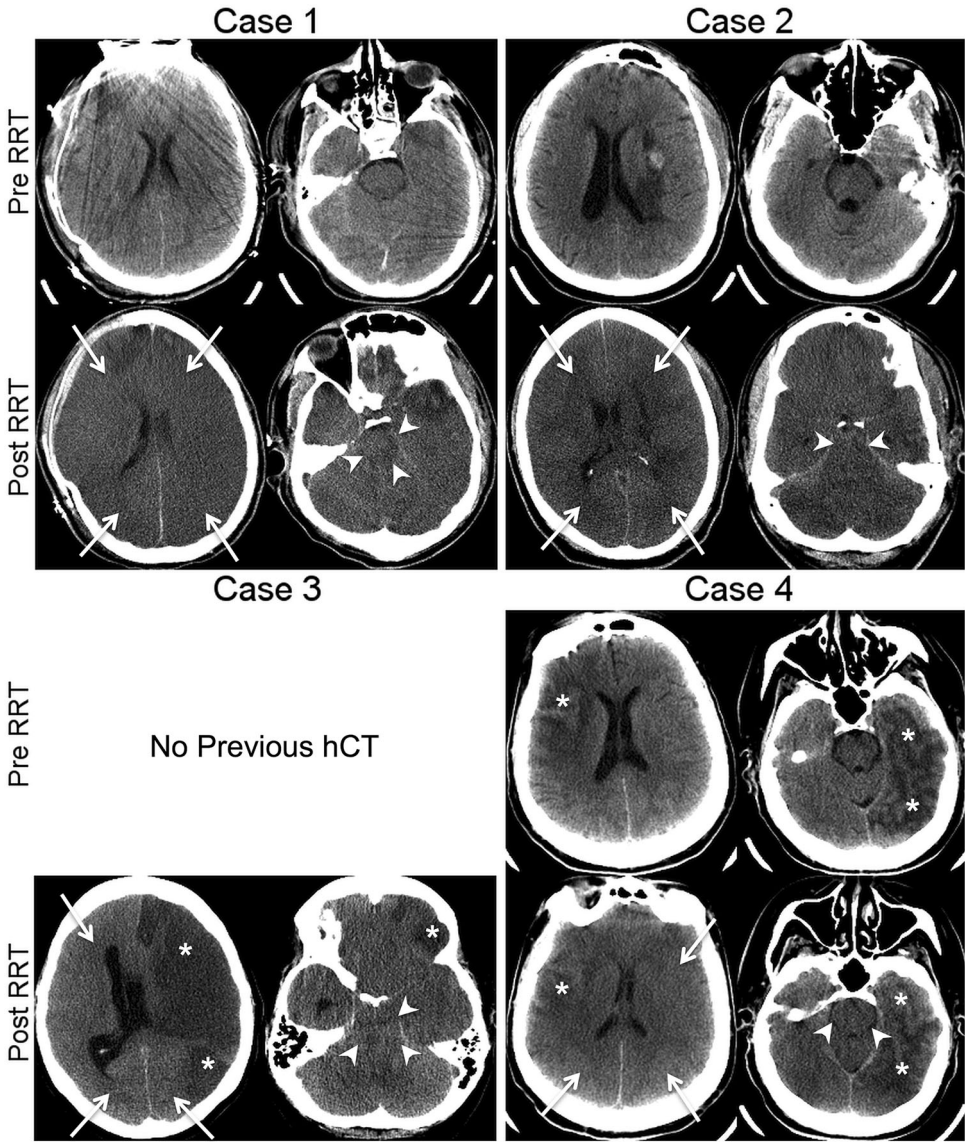

Fig. 1 Non-contrast HCT pre- and post-RRT for each case. Post-RRT images show loss of *gray–white* differentiation with sulcal effacement (*arrows*), as well as loss of cisternal spaces and brainstem herniation (*arrowheads*). In cases 3 and 4, the hypodense area represents subacute ischemic stroke (*asterisk*). As shown by the *arrows*, edema is not restricted to the side of the primary brain injury, but is also present in areas remote from it on the contralateral side, consistent with global edema not caused by the primary injury. *RRT* renal replacement therapy, *HCT* head computed tomography

reflexes. He was placed back on the ventilator. HCT immediately after the completion of the IRRT revealed very subtle brain edema, initially not noted by the clinical team. Six hours later, the pupils became fixed and 6 mm dilated with the loss of all brain stem reflexes. Immediate osmotherapy did not improve the patient's exam. Repeat HCT revealed global edema with brainstem herniation (Fig. 1). Notably, his BUN had decreased from 141 to 54 mg/dL in one session (Fig. 2).

Case 3

A 50-year-old woman was admitted to an affiliated teaching hospital with peritonitis due to perforated colon. After colectomy, sigmoid resection, and colostomy, she proceeded to a general surgical ICU where she suffered respiratory failure and severe septic shock requiring vasopressors. She was pharmacologically paralyzed to facilitate ventilator synchrony, thereby limiting the neurological examination to the pupillary exam. Prior to paralysis while on sedation with continuous fentanyl and midazolam infusions, she had 3-mm reactive pupils without spontaneous extremity movements. A detailed neurological examination was not performed prior to paralysis due to the severity of her septic shock. She suffered acute renal failure (sCreat 2.64 mg/dL) and was started on daily IRRT, as CVVH was not available at this hospital. After her 2nd IRRT treatment, she was weaned off vasopressors, paralysis, and sedation. Within 3 h after her 3rd IRRT treatment, she unexpectedly became apneic with fixed and 5-mm dilated pupils, and briefly hypotensive to SBP 80 mmHg (for about 1 min), requiring immediate reinitiation of vasopressors and resolution of the transient hypotension. Osmotherapy with mannitol or hypertonic

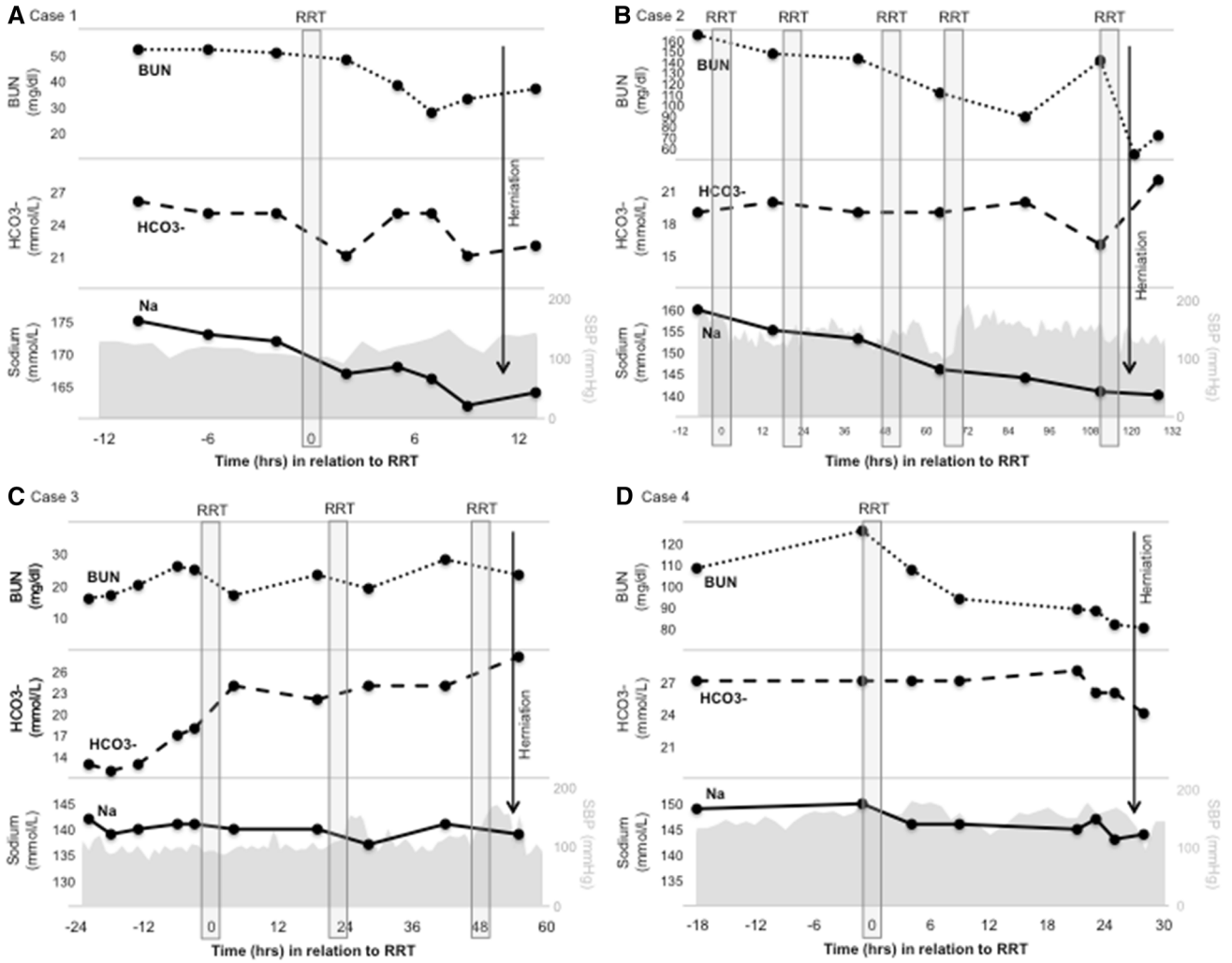

Fig. 2 Laboratory values and systolic blood pressures for each case leading to the herniation. On the *X*-axis, time is displayed in hours. The time point 0 represents the time of the first RRT. Negative values are hours pre-initial RRT, whereas positive values are hours post-initial RRT. *Boxes* mark each RRT without displaying the scaled duration of each RRT. The time of clinical herniation is marked with an *arrow*. When more than one SBP-value per hour was available, we displayed the lowest SBP in this graph so that potential hypotensive episodes were captured. BUN blood urea nitrogen, HCO_3^- serum bicarbonate, *SBP* systolic blood pressure

saline did not improve her pupillary reactivity. HCT revealed a large, previously unknown subacute left middle cerebral artery ischemic stroke, but in addition revealed significant global edema in the non-ischemic hemisphere out of proportion, with brainstem herniation (Fig. 1). She was not deemed a hemicraniectomy candidate due to her severe septic shock and global brain edema. She irreversibly lost all other brain stem reflexes within hours despite continued osmotherapy.

Case 4

A 52-year-old man with a history of atrial fibrillation, not of Coumadin, type 2 diabetes mellitus, and stage 4 chronic kidney disease (baseline sCreat 1.8 mg/dL), was admitted after IV thrombolysis for an acute right middle cerebral artery ischemic stroke. On hospital day 3, he additionally suffered a left posterior cerebral artery stroke (Fig. 1) and required intubation for airway protection. He received a tracheostomy, was intermittently following commands, and moving all four extremities with mild left arm weakness. Acute on chronic renal failure developed (sCreat 5.8 mg/dL; BUN 126 mg/dL), and CVVH was initiated on hospital day 16. Twenty-eight hours after starting CVVH, the patient experienced unexplained apneic episodes and was placed back on the ventilator. Within 1½ h, he suffered a witnessed PEA arrest, as noted by the ICU bedside nurse with cessation of the arterial line tracing. A "code blue" was called within seconds in the ICU. Advanced cardiac life support measures were instituted immediately (within 20 s) in the ICU with adequate chest compressions resulting in the return of spontaneous circulation (ROSC)

Table 1 Details of the renal replacement therapies for each case

	Dialyzer	Duration (h)	Dialysate flow (ml/min)	Blood flow (ml/min)	Dialysate sodium (mmol/L)	Serum sodium (mmol/L)
Case1						
CVVH	–	3.5	–	200	–	167
IRRT1		3	700	350	165	167
Case2						
IRRT1	Opti 160	2	500	220	160	160
IRRT2	Opti 160	2.5	500	300	155	155
IRRT3	Opti 160	3.5	500	400	153	153
IRRT4	Opti 160	3.5	500	350	150	146
IRRT5	Opti 160	4	500	350	141	141
Case3						
IRRT1	F 180	2.5	500	200	141	141
IRRT2	F 180	3	500	280	141	140
IRRT3	F 180	3	500	300	141	141
Case4						
CVVH		28	–	250	140	150

The renal replacement therapies were started slowly and increased across each treatment. Serum and dialysate sodium were matched to prevent rapid sodium shifts

CVVH continuous veno-venous hemofiltration, *IRRT* intermittent renal replacement therapy

within 5 min. Common causes for PEA were ruled out ("5T, 5H" [13]) by the treating neurointensivist's timely review of pre-PEA laboratory values, the arterial line, and continuous pulse-ox tracing. Immediately following this arrest, absence of all brain stem reflexes was noted. The patient was not immediately stable for transport, but HCT 6 h later revealed global brain edema and brain stem herniation (Fig. 1) without new areas of ischemia. By the judgment of an independent neuroradiologist and the treating neurointensivist, the degree of brain edema was deemed much more severe and advanced than would be expected within 6 h of a witnessed PEA arrest with immediate and adequate chest compressions, suggesting a different underlying cause for the brain edema, possibly precipitating the apneic events.

Death resulted in all patients, either from withdrawal of care or brain death.

Results

The details of RRT are displayed in Table 1. No anticoagulation was used during treatments. Serial laboratory studies and SBP for each patient are shown in Fig. 2. Throughout the RRT, all cases had only mild SBP fluctuations, and no patient had prolonged (>1 min) hypotension. In all cases, the dialysate sodium was matched to the sNa to prevent rapid sodium shifts. However, in case 1, the sNa decreased from 172 to 162 mmol/L during the single IRRT session. In cases 1 and 4, bicarbonate showed no significant decrease; case 2 had a rise in bicarbonate with RRT #5 (16 → 22 mEq/L); and case 3 had a rise in bicarbonate with the 1st RRT only (18 → 24 mEq/L). The URR ranged between 17 and 61 % across the patients' treatments. Case 1 had a URR of 45 % (BUN 51 → 28 mg/dl). In case 2, the URR ranged between 2 and 20 % during the first four treatments, but increased dramatically to 62 % (141 → 54 mg/dl) during the last treatment, when herniation occurred. Case 3 had a URR of 35 % (BUN 26 → 17 mg/dl), 17 % (BUN 23 → 19 mg/dl), and 18 % (BUN 28 → 23 mg/dl) across treatments. Case 4 had a URR of 35 % (BUN 126 → 80 mg/dl).

Discussion

We report, to our knowledge, the largest contemporary series of consecutive patients with acute brain injuries who suffered sudden global brain edema and herniation closely related in time to RRT without other identifiable causes for the neurologic deterioration. This suggests an association between RRT and brain edema in these neurocritically ill patients.

RRT was carried out using published expert recommendations for the management of neurologically injured patients [10, 14], except in Case 3 who was not known to have neurologic injury and in Case 1 in whom CVVH was

attempted but changed to IRRT due to persistent severe hyperkalemia. Common clinical symptoms in all patients included sudden apnea and fixed and dilated pupils, consistent with medullary and mesencephalic compression, all within 3 h of RRT termination. None of the patients had clinical improvement with the use of aggressive, high-dose osmotherapy and all had a fatal outcome. Common radiological features on HCT include global edema remote from and out of proportion to the area of initial brain injury and brain stem herniation.

In case 1, the 10-point decrease in sNa may have possibly contributed to the development of brain edema immediately following IRRT. A high dialysate sodium (165 mmol/L) was chosen for this case with the aim to prevent a rapid decrease in sNa [10], but we must consider that an even higher dialysate sodium may have possibly prevented the observed decrease. In our three other cases, however, an acute decrease in sNa was not observed, leaving room for an additional explanation for their sudden brain edema. A review of the literature suggests that our patients' deteriorations closely resemble those described in previous case reports of DDS [9]. First described in 1962 [5], severe DDS was observed in a small number of patients on IRRT who were suffering from severe sepsis or neurologic injury [16]. To our knowledge, five cases of severe DDS [1, 2, 17] were published before 1987. Three of these cases had underlying neurologic injury [2, 17], suggesting a predisposition to the development of DDS. However, since that time, there have been no further reports of severe DDS in neurologically injured patients.

Radiological and autopsy studies in patients who had suffered DDS have provided evidence for brain edema with DDS [4, 5, 18]. Studies in chronic kidney disease patients undergoing HCT and brain MRI pre- and post-IRRT showed that the brain edema immediately following IRRT is vasogenic and not cytotoxic in nature [19, 20].

The exact pathomechanisms for DDS remain unclear, but three explanations have been proposed: "reverse urea effect" [11, 21], "idiogenic osmoles hypothesis" [22], and "paradoxical brain acidosis" [23]. Kennedy et al. first suggested the "reverse urea effect" after it was noted in a mouse model that urea was removed more slowly from cerebral spinal fluid than from blood during IRRT [15]. IRRT leads to a rapid reduction in plasma urea with delay in the brain urea clearance [11, 21, 24, 25], creating an osmotic gradient between the plasma and brain [11]. The discovery of urea transporters further supported the "reverse urea effect" [11], because these transporters are downregulated in uremic states, thereby decreasing the ability of the brain to quickly adapt to the plasma urea loss [26]. While one case suggests that urea must be very elevated (>100 mg/dl) and must drop by >50 % to cause brain edema from DDS [4], a different case showed that even smaller shifts in urea (17 % in 2 h) can lead to DDS-induced brain edema [9]. Other studies, initially in dogs and later in traumatic brain injury and neurosurgical patients, have revealed an increase in intracranial pressure during IRRT regardless of the degree of urea reduction [6, 17, 27]. Furthermore, aquaporin channels are upregulated in uremic animals, facilitating movement of water into the brain [28]. This concomitant alteration in both the aquaporin and urea channels may allow smaller urea gradients to lead to larger than expected water shifts in the brain [29], as seen in our four patients.

The second proposed mechanism of DDS, the "idiogenic osmoles hypothesis", suggests that dialysis may generate other, but thus far unidentified, osmotically active molecules that contribute to brain edema [22, 23]. The basis for this hypothesis was generated by experiments in various animal models which revealed that the gradient created by loss of urea is insufficient to account for the brain edema noted in these experiments [22].

Finally, "paradoxical brain acidosis" potentially leading to DDS rests on observations in uremic animals undergoing RRT [23]. In these animals, as RRT corrected the acidosis, brain pH decreased, thereby creating an osmotic gradient by displacement of intracellularly protein-bound potassium and sodium. Consequently, these ions become osmotically active causing influx of water [30]. Of note, two of our patients had increases in bicarbonate during RRT, possibly implicating paradoxical brain acidosis as a cause of their deterioration.

Patients with acute neurological injuries may be particularly at risk for brain edema when undergoing IRRT; the expression of aquaporin channels is upregulated in uremia [28] as well as various forms of acute brain injury [31, 32]. This "double-detrimental" effect of uremia further explains the predisposition of these patients to brain edema following IRRT [33].

Changes in the relationship between the initiation of IRRT and surges in ICP, likely due to impaired cerebral autoregulation, have been previously demonstrated in a case report [8] with a similar neurological injury as in our case 2. We were limited in the assessment of ICP due to the lack of ICP monitors in all of our cases, as RRT was initiated after the acute brain edema period. Therefore, we cannot fully exclude that persistent impairment in cerebral autoregulation and small MAP fluctuations during IRRT may have contributed to the development of global edema. While CVVH reportedly did not result in ICP surges in the other case [8], we observed the development of global edema even after CVVH, suggesting that perhaps impaired autoregulation is not the sole explanation for the brain edema.

It is unlikely that our patients deteriorated due to "rebound edema" from sudden osmotherapy withdrawal,

as all patients had been weaned off osmotherapy for several days prior to starting RRT, or had never received osmotherapy (case 3). Plasma osmolality before and after RRT was not available, because per our clinical routine, osmolality, and osmolar gaps are only checked when patients are receiving mannitol.

Our cases affirm in a contemporary cohort that even with current IRRT methods with a high sodium dialysate, or CVVH as recommended by experts for RRT in neurologically injured patients [10, 14], rapidly progressive brain edema can occur, even after several rounds of IRRT. We also report the first possible case of brain edema and death with CVVH, which is considered the safer alternative to IRRT in patients with acute neurological injury [10, 34]. Our cases support that patients with acute neurological injuries may be particularly at risk for brain edema when undergoing IRRT.

While we cannot prove a clear and single mechanism for the deterioration in our patients, the literature provides several plausible mechanisms for the observed brain edema, most convincingly DDS by way of urea reduction and paradoxical brain acidosis. We call for the establishment of RRT guidelines in neurocritically ill patients with acute renal failure. In the meantime, we recommend refraining from IRRT, using continuous RRT methods only, using a very high sodium dialysate with close monitoring of the sNa, BUN, bicarbonate, neurological exam, and continuous monitoring of blood pressure and oxygenation.

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Conflict of interest Marcey Osgood, Rebecca Compton, Raphael Carandang, Wiley Hall, Glenn Kershaw and Susanne Muehlschlegel have no conflict of interest.

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