

Brain injury and the kidney

Dilip K. Kulkarni

INTRODUCTION

Brain injury affects kidney function and kidney injury affects brain; is it a cross-correlation or interconnection or a vicious cycle?

Afferent impulses from central nervous system (CNS) regulate renal blood flow, glomerular filtration rate and renal sodium handling.^[1] On the other hand, impulses originating from the kidney are carried via unmyelinated and thinly myelinated fibres to the CNS and the contralateral kidney to regulate CNS activity and coordinate renal sodium handling.

Both organs have a common feature of a tight auto-regulatory mechanism that maintains constant blood flow over a wide range of blood pressures. It is unclear whether these mechanisms are interconnected.^[2]

The incidence of acute renal dysfunction and renal failure after cerebral injury is diversely reported to be ranging from 8% to 23% and 0.5% to 0.8%, respectively, in different studies.^[2]

Renal problems can occur in various acute cerebral insults such as cerebral ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, head injury and white matter lesions.^[3-5]

HOW BRAIN INJURY HAS ITS EFFECT ON KIDNEY

The brain injury can influence the kidney function by following main mechanisms: Neuro-inflammation, increased neuro-sympathetic activity and through hypothalamo-pituitary axis [Figure 1].^[3]

Department of Anaesthesiology and Intensive Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Neuro-inflammation

Brain injury activates an inflammatory response, the intensity of which is related to the degree of the primary injury and subsequent secondary insults.^[6] The complex cascade of inflammatory events following brain injury is mediated by the production and activation of complements, cytokines, adhesion molecules and other multifunctional peptides. Cells of the CNS are an abundant source of inflammatory mediators,^[7,8] and CNS expression of pro-inflammatory cytokines and complement components leads to recruitment of neutrophils and monocytes (macrophages) across the blood-brain barrier (BBB) and enhancement of the established neuro-inflammation.^[9]

Intracranial inflammatory mediators pass into the systemic circulation via a dysfunctional BBB,^[10] and elevated levels of cytokines are present in plasma as well as cerebrospinal fluid after brain injury.^[6] They mediate systemic changes such as fever, neutrophilia, muscle breakdown, altered amino acid metabolism, production of hepatic acute phase reactants and altered endothelial permeability.^[11]

The systemic effects of neuro-inflammation are also mediated by neuroendocrine pathways, such as the hypothalamic-pituitary-adrenal axis, and the autonomic nervous system.^[11,12] Dysfunction of these pathways may contribute to the immuno-depression associated with severe brain injury. Intracranial hypertension causes interleukin-10 (IL-10) to be released from peripheral monocytes, and the resultant immunodepression can be blocked by systemic β adrenergic blockade.^[13] Endogenous catecholamines also cause a selective suppression of cellular immunity through immuno-inhibitory cytokines.^[14] Finally, the stress-induced hypermetabolic response may also contribute to the immunocompromised state after brain injury.^[15]

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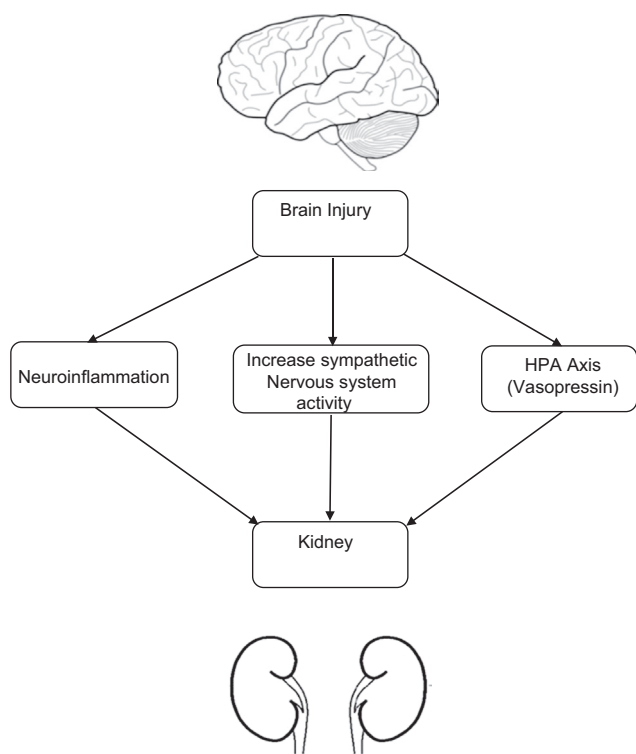


Figure 1: Schematic representation of different mechanisms by which brain injury affects the kidney

The overall effect of these different mechanisms is depression of the immune system^[11] and suppression of cell-mediated immunity.^[16] Infection is therefore a significant complication and occurs in 50–65% of brain injury patients with almost half of the infections occurring in the lower respiratory tract.^[16,17]

Like in sepsis, the systemic inflammatory response triggered by cytokines plays a central role in the pathogenesis of multiple organ dysfunction and failure.^[18]

Increased sympathetic activity

Acute brain injury often increases sympathetic nervous system activity and plasma catecholamines resulting in systolic hypertension. The increased visceral sympathetic nervous system activation results in reduced renal glomerular perfusion with increased renal sodium reabsorption. Sustained severe hypertension can lead to red cell fragmentation, haemolysis and acute kidney injury (AKI) secondary to red cell thrombi in the glomeruli.^[4]

Hypothalamo-pituitary axis

Acute cerebral injury can lead to acute changes in renal sodium handling due both to changes in vasopressin secretion and to cerebral sodium wasting.

The electrolyte and fluid disturbances can profoundly affect morbidity and mortality in brain-injured patients.

The common electrolyte imbalances are associated with the hypothalamic-pituitary axis dysfunction are central neurogenic diabetes insipidus, syndrome of inappropriate secretion of antidiuretic hormone and cerebral salt-wasting syndrome. The details of these conditions are given in Table 1.^[19]

Other factors such as haemodynamic instability during brain injury, use of mannitol, antibiotics and radiocontrast solutions can affect kidney function.^[4]

HOW KIDNEY HAS ITS EFFECT ON BRAIN

The kidney can cause neurological disturbance by different mechanisms such as systemic inflammation, increase catecholamines, uraemia, hyperosmolar state and acidaemia [Figure 2]. The cause of neurological disturbance is often multifactorial.^[20]

Effect of systemic inflammation induced by acute kidney injury on the brain

The systemic inflammatory response in AKI can start within minutes after renal ischaemia.^[21] The first there is sudden increase in uric acid, a marker and mediator of renal ischaemic injury, triggering a secondary response, characterised by the exocytosis of Weibel–Palade bodies, releasing their pro-inflammatory mediators including endothelin-1, large multimers of von Willebrand factor, IL-8 and angiopoietin-2. Direct activation of the innate immune system produces potent cytokine-like mediators in the systemic circulation, leads to an intense inflammatory response within hours of ischaemic renal injury.^[21]

The inflammatory response observed in AKI leads to disruption of the BBB, endothelial injury and stimulation of the inflammatory and coagulation cascades within the brain leading to changes in neuronal cell protein transcription and cellular activation, altering the cerebral function.^[20]

Changes in cerebral neurotransmitters

Decreased cerebral norepinephrine, epinephrine and dopamine may lead to impaired locomotor activity. Derangements in the metabolism of neurotransmitters may variably disrupt cerebral function, ranging from coma to hyperexcitation states. Renal sympathetic nervous system over activity has been reported to increase the risk of hypertension and the development of the posterior reversible encephalopathy syndrome due to ischaemic injury and oedema in the medulla and cerebellum.^[22]

Acid–base disturbances

The kidney plays a key role in acid–base balance regulation, to allow optimal cellular metabolism and function. Metabolic acidosis occurs after AKI affects cerebral neuronal metabolism and may impair normal cerebral function.

Table 1: Comparison of central neurogenic diabetes insipidus, syndrome of inappropriate secretion of antidiuretic hormone and cerebral salt-wasting syndrome

| Features | Central neurogenic diabetes insipidus | Syndrome of inappropriate secretion of ADH | Cerebral salt-wasting syndrome |
|--------------------------------|---|--|---|
| Cause | Decreased secretion of ADH or renal unresponsive to ADH | Over-production of ADH | Renal sodium transport abnormality |
| Serum level of sodium mEq/L | Hyponatraemia >145 (high) | Hyponatraemia <135 (low) | Hyponatraemia <135 (low) |
| Serum osmolality, mOsm/kg | >295 (high) | <275 (low) | <275 (low) |
| Urinary osmolality, mOsm/kg | Decreased (<200) | Elevated (>100) | Elevated (>100) |
| Urinary level of sodium, mEq/L | Normal or decreased | Normal or elevated (>25) | Elevated (>25) |
| Urine output | Increased (>250 ml/h) | Decreased | Decreased |
| Urine specific gravity | <1.005 | >1.010 | >1.010 |
| Extracellular volume | Decreased | Increased | Decreased |
| Serum urea nitrogen | Elevated | Normal or low | Elevated |
| Mental status | Normal to impaired | Confusion | Agitation, decreased consciousness |
| Body weight | Decreased | Normal or increased | Decreased |
| Heart rate | Tachycardia | Slow or increased | Postural tachycardia |
| Blood pressure | Mild hypotension | Hypertension | Postural hypertension |
| Treatment | Fluid replacement, desmopressin or vasopressin | Fluid restriction, slow sodium replacement | No fluid restriction, slow sodium replacement |

ADH=Antidiuretic hormone

Intracellular acidosis leads to influx of both sodium and calcium into the cell and which leads to cellular injury and cell death.^[20]

Management of acute kidney injury in the patient with acute brain injury

Maintaining adequate hydration is an important clinical goal for preventing AKI, particularly for reducing the risk of contrast-induced nephropathy. In addition, multiple contrast exposure should be minimised by selecting other imaging techniques wherever possible, and nephrotoxic drugs should be similarly avoided if possible.^[20]

Although renal replacement therapy can help improve encephalopathy due to uraemia, by removing azotaemic retention products and reducing toxic drug levels, too rapid a fall in serum urea may paradoxically cause cerebral oedema.^[23,24]

Intermittent haemodialysis using high-efficiency dialysers coupled with dialysates containing supra-physiological levels of bicarbonate can exacerbate underlying brain damage. The rapid increase in blood pH during dialysis sets up a disequilibrium; as bicarbonate is charged it only slowly crosses into cells, whereas the reaction between bicarbonate and hydrogen ions in plasma water leads to

carbon dioxide, which rapidly transverses lipid-rich cell membranes and once inside cells generates hydrogen ions, generating a paradoxical intracellular acidosis, which itself leads to generation of intracellular idiogenic osmoles, so increasing osmolality further and increasing water entry leading to cerebral oedema.^[24]

Peritoneal dialysis is a continuous renal replacement therapy and, although associated with slower solute clearances than haemodialysis, can also lead to an increase in brain swelling in brain-injured patients, as all commercial dialysates are hyponatraemic and risk exacerbating hyperglycaemia due to the high glucose content.^[25,26]

For patients who develop progressive AKI requiring renal replacement therapy, modifying the dialysis prescription may minimise further brain injury. These modifications should include continuous renal replacement therapy or intermittent haemodialysis with reduced blood flow rate, a longer daily dialysis session time in combination with smaller surface area biocompatible dialysers and cooled dialysate with increased sodium and reduced bicarbonate dialysate concentrations.^[27,28]

To conclude in one sentence, brain injury can significantly alter the kidney function and vice versa.

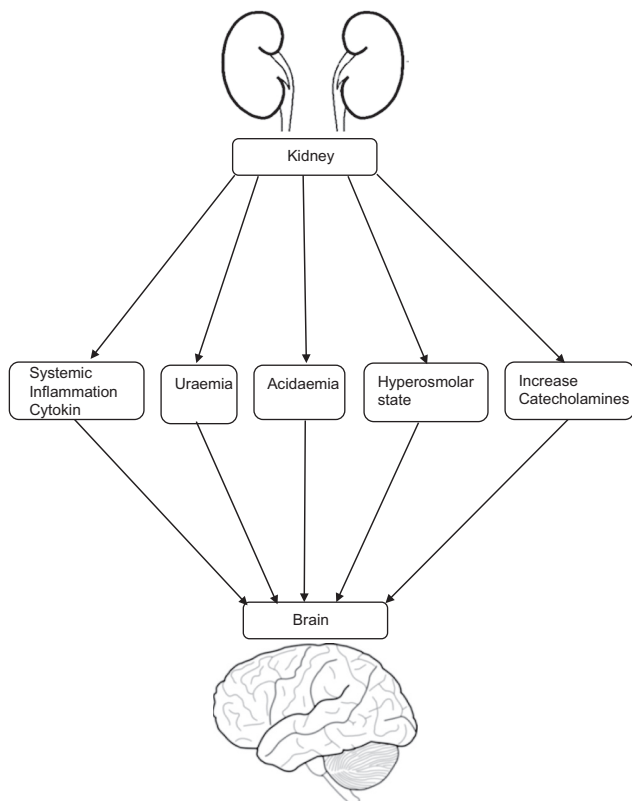


Figure 2: Schematic representation of different mechanisms by which kidney dysfunction affects the brain

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Conflicts of interest

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