

REVIEW

Systemic consequences of neurological catastrophes at the ICU: focus on aneurysmal subarachnoid haemorrhage

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Abstract - Extracerebral organ dysfunction occurs frequently after severe brain injury and is associated with mortality and poor functional outcome. Cardiac and pulmonary complications are common, especially after aneurysmal subarachnoid haemorrhage. The exact causes of neurogenic myocardial dysfunction and pulmonary oedema after severe brain injury remain to be elucidated, but hyperactivity of the sympathetic nervous system and a systemic inflammatory response have both been implicated in its development.

Hyponatraemia is the most frequent metabolic derangement seen after traumatic and non-traumatic brain injury. Both the syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting have been described as the causal mechanism. In this review we will give an overview of the epidemiology, pathophysiology, and treatment options for neurogenic pulmonary oedema, cardiac dysfunction, and hyponatraemia after severe acute brain injury with a main focus on aneurysmal subarachnoid haemorrhage, and describe some insights regarding systemic inflammatory response syndrome in these patients.

Keywords - Stress cardiomyopathy, neurogenic pulmonary oedema, cerebral salt wasting

Introduction

Neurological catastrophes such as aneurysmal subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH), and severe traumatic brain injury (TBI) are common and frequently devastating conditions encountered in the ICU. The prognosis of severe acute brain injury caused by these conditions is largely determined both by the initial insult and the development of secondary intracranial complications such as neuronal hypoxia. Delayed cerebral ischaemia (DCI) and rebleeding are associated with serious morbidity and increased mortality after aneurysmal SAH; cerebral hypoperfusion and ischaemia after severe TBI have similarly been associated with adverse outcome [1-4]. Cerebral ischaemia or hypoperfusion may be the result of secondary systemic insults such as pneumonia or sepsis in the face of disturbed cerebral vascular autoregulation, and have been related to poor outcome and mortality [5-7]. In addition, especially after SAH, extracerebral complications may also develop as a direct consequence of brain injury, including electrolyte derangements (especially hyponatraemia), a systemic inflammatory response syndrome (SIRS), and neurogenic cardiac and pulmonary dysfunction [7].

The aim of this review is to provide a practical and historical overview of the pathophysiology and management of these major systemic sequelae of neurological catastrophes that may be encountered in the ICU.

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Pulmonary oedema

Pulmonary complications have been reported in up to 30% of patients after acute severe brain injury [8]. Post-mortem studies of patients with intracranial pathology recorded incidences of pulmonary oedema of up to 90% [9]. The development of pulmonary dysfunction in patients with isolated brain injury has been associated with prolonged intensive care stay, poor functional outcome, and death [8,10,11]. Neurogenic pulmonary oedema is defined as the development of acute pulmonary oedema shortly after a neurologic insult, and has been reported in various pathologies of the central nervous system [12]. The diagnosis is made based on clinical signs such as dyspnoea, tachypnoea, pulmonary crackles, and hypoxaemia after an acute neurological catastrophe with the presence of characteristic bilateral pulmonary infiltrates on chest X-ray and presumed absence of a cardiac or infectious origin of pulmonary oedema.

Pathophysiology

Different pathophysiological mechanisms in neurogenic pulmonary oedema have been suggested. In general, it is presumed to be triggered by an acute increase in intracranial pressure (ICP) and/ or ischaemic insults stimulating suspected pulmonary oedema trigger zones of the brain, the existence of which have been corroborated in animal studies [13-16]. These intracranial trigger zones are mainly located in the posterior hypothalamus and in the medulla oblongata, where ischaemia or haemorrhage may induce major sympathetic activation.

Early animal studies showed that bilateral preoptic lesions can cause fatal haemorrhagic pulmonary oedema through a disinhibition phenomenon of the oedemagenic regions of

the hypothalamus in rats [15]. Moreover, splanchnectomy protected these animals from the effects of preoptic lesions, and therefore it has been suggested that the splanchnic sympathetic overstimulation in acute brain injury may cause major fluid shifts from the splanchnic to the thoracic vascular compartment due to splanchnic vasoconstriction, contributing to pulmonary oedema [14].

The increase in pulmonary pressures eventually causes injury to the basement membranes and endothelium of alveolar capillaries, causing leakage of cells and proteins into the alveolar spaces (high-permeability oedema) [16]. In addition, the supraphysiologic sympathetic drive may also provoke cardiac dysfunction, leading to increased left atrial pressures and pulmonary congestion, or may result in acute severe pulmonary venous vasoconstriction without increase in left atrial pressure [17]. Further, cerebellar haematoma has repeatedly been reported to cause fulminant pulmonary oedema, presumably due to mechanical disruption of the area of the dorsal motor vagus nucleus in the dorsal medulla, thereby disturbing the parasympathetic/sympathetic balance in favour of the sympathetic side followed by pulmonary oedema (see figure 1). Clinical studies support the finding that pulmonary oedema trigger zones recede in the brainstem because posterior circulation aneurysmal SAH has been associated with a higher

incidence of neurogenic pulmonary oedema than anterior circulation SAH, presumably due to brainstem compression in the first [18].

The above-mentioned haemodynamic/neurogenic mechanism has also been referred to as the “blast injury” theory, and proposes a surge of catecholamines after a sudden increase in ICP, ischaemia, or trauma to the hypothalamus or medulla. Further, a SIRS may contribute to capillary leakage in the lungs. We will further elucidate this in the section on SIRS. In the end, the clinical picture of acute lung injury after brain damage may be explained by a “double-hit” model: a first hit caused by the sympathetic storm which is associated with hydrostatic pulmonary oedema, and a simultaneous inflammatory response causing the development of neurogenic pulmonary oedema, which makes the lungs vulnerable to secondary insults such as infection and ventilator-induced lung injury that may finally result in the development of acute lung injury (ALI) or ARDS [8].

Management

Treatment of pulmonary oedema should be aimed at appropriate gas exchange to prevent secondary brain injury due to severe hypoxaemia. Mechanical ventilation is the main supportive therapy during acute respiratory failure in patients with severe brain injury, although the protective ventilatory strategy (aiming at low tidal volume and limited plateau pressure) may be somewhat challenging without permissive hypercapnia, which may cause a rise in ICP. If necessary, PEEP may be safely applied, as its influence on MAP and CPP (cerebral perfusion pressure) is usually limited [19]. Dobutamine may also have beneficial effects on pulmonary oedema in combination with cardiac dysfunction, and does not compromise cerebral perfusion [20]. Recently, Hoff et al. showed that SAH patients who have neurogenic pulmonary oedema have lower blood volume than those who do not [21]. Therefore, diuretics should be used carefully to prevent further intravascular volume depletion, which predisposes to DCI in the case of SAH. Guided fluid management (e.g. by daily blood volume measurements or invasive haemodynamic monitoring) may result in less hypovolemia and less hypervolemia (and concomitant pulmonary oedema) after SAH [22-24].

Although the mortality rate of neurogenic pulmonary oedema is high, symptoms may resolve rapidly with correct management, starting with early and appropriate treatment of the underlying neurological cause.

Cardiac injury

Stress cardiomyopathy, also known as neurogenic stunned myocardium, is a term used to describe a decrease in cardiac function caused by acute sympathetic stress, which may be caused by intracranial pathology. Stress cardiomyopathy after acute brain injury has long been recognized, and is very diverse in its presentation. Regional wall-motion abnormalities, ECG abnormalities, and elevated biochemical markers of myocardial damage have frequently been reported in various forms of brain injury. A recent meta-analysis showed that markers for cardiac

Figure 1. Functional anatomy of neurogenic pulmonary oedema

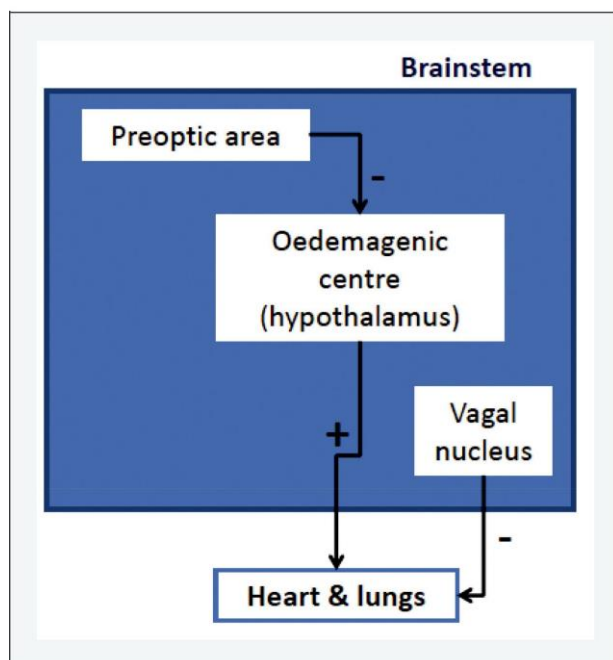


Figure legend. Proposed regulatory pathway to explain the occurrence of neurogenic pulmonary oedema, based on animal experiments and clinical data in humans (see text). Preoptic area dysfunction or vagal nucleus dysfunction will result in disinhibition of the hypothalamic oedemagenous centre or inhibition of the vagal input on the cardiorespiratory system respectively, resulting in sympathetic “overdrive.”

damage and dysfunction were associated with poor neurological outcome, DCI, and increased mortality after SAH [25].

Echocardiographic studies have shown systolic regional wall-motion abnormalities with impaired left ventricular performance in up to a quarter of SAH patients [25,26]. Diverse patterns of regional wall-motion abnormalities have been described with the similarity that they all extend beyond the normal distribution pattern of a single coronary vessel. Some wall-motion abnormalities affect the basal parts and some predominantly affect the apex (apical ballooning syndrome, or "Takotsubo cardiomyopathy") [27]. These wall-motion abnormalities are temporary, but not always without clinical consequence [25]. Ventricular failure may occur, which may be associated with an increased risk of DCI after SAH [26].

ECG abnormalities are almost universal following acute brain injury, with incidences reported of between 50% and 100% for SAH, between 60% and 70% for intracerebral haemorrhage, and between 15% and 40% for ischaemic stroke [28]. Common repolarization abnormalities are inverted T-waves, ST depression or elevation, and QT interval prolongation. Clinically important arrhythmias such as atrial tachyarrhythmias and ventricular arrhythmias are reported in 1% to 4% of SAH patients [29]. These arrhythmias were significantly related to increased risk of cardiovascular comorbidity, length of hospital stay, poor outcome, and death [29]; however, in other studies this relationship was not consistent [11,28].

Serum markers of cardiac injury are frequently increased after acute brain injury. The frequency of elevated serum cardiac Troponin-I (cTI) in SAH has been reported to be between 20% and 40% [30]. Increased levels of cTI after SAH have been associated with systolic and diastolic cardiac dysfunction, ALI, DCI, poor functional outcome, length of ICU stay, and mortality [31]. Increased plasma creatine phosphokinase-myocardial fraction (CK-MB) concentration is also observed after SAH, especially in patients with echocardiographic evidence of wall-motion abnormalities [32]. In addition, elevated serum B-type natriuretic peptide (BNP) levels after SAH have been associated with myocardial necrosis, pulmonary oedema, and both systolic and diastolic dysfunction of the left ventricle [33].

Pathophysiology

The most widely accepted theory for cardiac dysfunction is the "catecholamine hypothesis" in which acute brain injury leads to activation of the sympathetic nervous system as a consequence of brainstem ischaemia or damage to the insular cortex [34,35]. The pathogenesis of stress cardiomyopathy may differ from neurogenic pulmonary oedema in that the first may be exaggerated by extreme hypertension, and that the insular cortex may play a role in its development. Ischaemia of the brainstem (including the medulla oblongata), hypothalamic, or insular cortex lesions may lead to unopposed sympathetic stimulation, resulting in elevated circulating and local levels of catecholamines [36]. Local norepinephrine release at the myocardial interstitium from the sympathetic nerve terminals in the myocardium leads to myocyte necrosis and contractile dysfunction through

intracellular calcium overload and production of oxygen-derived free radicals, indicating that the sympathetic nerve terminals play a pivotal role in stress cardiomyopathy. This has been corroborated in animal models where cardiac abnormalities still occurred in adrenalectomized animals (indicating that systemic catecholamine release is not essential in stress cardiomyopathy) but not in sympathectomized animals [37,38]. The classical pathological finding in the myocardium of neurological patients is focal contraction band necrosis, also referred to as myocytolysis or myofibrillary degeneration, subendocardial congestion, and haemorrhages [39].

Management

Treatment of myocardial dysfunction is mainly supportive, as the condition will normally improve over time. However, hypervolemia may lead to pulmonary congestion and congestive heart failure in patients with cardiac dysfunction. When in doubt about the balance between volume status and cardiac contractility in these patients, goal-directed haemodynamic monitoring may be warranted, either by using a pulmonary artery catheter or guided by transpulmonary thermodilution [24], aiming for normovolaemia. Of note, normovolaemia in the case of SAH should aim for optimization of cerebral perfusion and oxygen delivery, and in that sense the goal of haemodynamic optimization may differ from septic patients, for example. In SAH patients with reduced cardiac output, haemodynamic support may be helpful to minimize the risk of developing DCI [26]. Treatment with inotropic agents such as dobutamine and phosphodiesterase inhibitors (milrinone) has been reported to be beneficial to increase cardiac performance in SAH patients with cardiac dysfunction [40]. Pharmacological α - and β -blockade may normalize ECG changes in some patients after SAH, but published reports to date are inconclusive with regard to clinical benefit [41].

Systemic inflammatory response syndrome (SIRS)

Various symptoms of SIRS have been reported after acute brain injury, including body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate $>120/\text{bpm}$, respiratory rate $>20/\text{min}$, or white blood cell count $<4000/\text{mm}^3$ or $>12000/\text{mm}^3$ [6,7,42]. In one study, over 54% of SAH patients met two or more of the SIRS criteria, which was significantly related to poor clinical grade, poorer outcome, and increased risk of complications [43]. In a recent study by Tam et al., the incidence of SIRS after SAH was even higher (63%), and was associated with poor outcome but not with vasospasm or DCI [44]. Gruber et al. found that a confirmed infection was only present in 30% of all SAH patients with SIRS, suggesting another non-infectious mechanism behind systemic inflammation after brain injury [6].

There is emerging evidence for increased intracranial production of pro-inflammatory cytokines after brain damage causing secondary injury to the brain [45]. After disruption of the blood-brain barrier, these cytokines may leak into the systemic circulation and cause stimulation of target cells in peripheral organs, resulting in a local and systemic inflammatory response [46]. The development of this inflammatory response without

infection has been associated with poorer outcome in both stroke and SAH [43,47].

Furthermore, the sympathetic storm after a cerebral insult may also initiate a direct inflammatory effect and local cytokine expression caused by the increased hydrostatic pressure in the lungs [48]. This inflammatory effect further increases the risk of pulmonary oedema [12,46]. This interaction between the brain and the immune system after major (brain) injury is also known as the neuroendocrine response [49,50]. Lymphoid organs receive extensive sympathetic innervation and norepinephrine can act as neurotransmitter with either immunostimulatory or immunosuppressive effects. Increased levels of pro-inflammatory cytokines have been measured after SAH and TBI [45,51]. Naredi et al. showed increased levels of pro-inflammatory markers C3a, C5b-9, and IL-6 up to 72 hours after SAH [52]. However, in patients with a "sympathetic storm" after brain injury, a rapid systemic release of the immune-inhibitory cytokine, interleukin-10, has also been demonstrated [53]. Although systemic signs of inflammation have been objectively shown to occur after acute brain injury, as mentioned in this section, some SIRS criteria (e.g. tachycardia) may also in be fulfilled through the sympathetic activation itself. Therefore, SIRS may also have beneficial effects such as increased cardiac output leading to increased cerebral blood flow in a circulatory compromised brain. However, we could not find data indicating beneficial effects of systemic inflammation, for instance, as measured by pro-inflammatory markers in acute brain injury or SAH. In conclusion, although SIRS has been shown to occur after neurologic catastrophes, and has mostly been associated with adverse outcomes, its exact clinical significance remains to be elucidated.

Hyponatraemia

Hyponatraemia, defined as a plasma sodium (Na⁺) level of less than 135 mmol/l, is the most common electrolyte disorder encountered in acute brain disease, and has been reported in up to 30% of patients with recent SAH [54]. Plasma sodium is usually mildly to moderately decreased (120-130 mmol/l), but

may occasionally be severely decreased (<120 mmol/l) [55]. Accompanying symptoms include seizures and mental status changes, ranging from confusion and lethargy to coma and death. In SAH patients, hyponatraemia is clearly associated with increased incidence of cerebral ischaemia [54].

Pathophysiology

The pathophysiology of hyponatraemia in acute brain disease is not well understood, and has been the subject of considerable debate. At least two aetiologies have been suggested: the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW). SIADH and CSW are both characterized by hyponatraemia with low plasma osmolality, high urine osmolality, and sodium excretion in the absence of adrenal, renal, or thyroid disease. The key feature differentiating between the two entities is the presence of decreased extracellular volume in CSW and normal or increased extracellular volume in SIADH (Table 1) [55,56].

The term CSW was used in the 1950s, as excessive natriuresis was observed in patients with various brain diseases [57]. With the discovery of antidiuretic hormone (ADH), SIADH became the favoured causal mechanism [58,59]. In recent years, evidence has accumulated implicating CSW as the most common cause of hyponatraemia in acute brain disease.

Studies in neurosurgical and SAH patients have shown that the majority of patients with acute brain disease tend to have a decreased circulating volume, expressed by weight loss, decreased total blood and plasma volume, low venous pressure, and need for increased fluid intake to prevent a negative fluid balance, which is compatible with CSW [60-62]. At the same time, some studies and case reports have clearly documented SIADH as the cause of hyponatraemia in intracranial disease [58,59,63,64]. Determining the aetiology of hyponatraemia has important implications for treatment, since fluid restriction, which is appropriate for SIADH treatment, could further aggravate volume deficit and cerebral ischaemia in CSW [65].

Several studies have shown elevated levels of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) after SAH, which may be a suitable explanation for the proposed natriuresis [63,66,67]. Secretion of ANP may in fact be a protective mechanism against raised ICP and cerebral oedema by regulating cerebrospinal fluid (CSF) production and natriuresis, and the water and sodium content of the brain [68]. In addition, pressure-induced sodium and water excretion, due to increased sympathetic central nervous system activity, may also contribute to a reduction in circulating blood volumes after SAH [69]. Finally, inadequate activation of the renin-angiotensin-aldosterone system in response to hypovolaemia and high sympathetic tone has also been described as a possible cause of increased natriuresis after SAH [70].

Management

Treatment should be started with intravenous supplementation of isotonic or hypertonic sodium solution or oral salt capsules, assuming CSW as the most likely cause of hyponatraemia,

Table 1. Differential diagnostic criteria for cerebral salt wasting (CSW) and syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH).

	CSW	SIADH
Serum sodium, mmol/l	<135 (both)	
Urine sodium, mmol/l	>100	>25
Serum osmolality, mOsm/kg	>270	<270
Urine osmolality, mOsm/kg	>150 (both)	
Fluid balance	Negative	Positive
Signs of dehydration	Variable	Absent
Central venous pressure	↓	↑ or normal
Serum Urea	↑	↓

especially in SAH where precipitation of hypovolaemia is strongly associated with cerebral ischaemia. Worsening of hyponatraemia after a fluid bolus of 500-1000 ml of 0.9% NaCl warrants careful reconsideration of the diagnosis. Furthermore, mineralocorticoids have been reported to attenuate natriuresis. Fludrocortisone has been shown to prevent intravascular volume depletion and reduce frequency of negative sodium balance in patients with SAH [71]. More recently, Katayama et al. demonstrated that hydrocortisone prevented excess natriuresis and hyponatraemia in patients with SAH [72]. Therefore, fludrocortisone (especially if there is concomitant hyponatraemia) or hydrocortisone may be considered as treatment for excessive natriuresis resulting in negative fluid balances, although evidence indicating a positive effect on outcome does not exist.

Conclusion

Severe brain injury encountered at the ICU may present with variable disturbances of both intracranial and systemic physiology. Neurogenic extracerebral organ dysfunction (i.e.

as a direct consequence of the neurological injury) occurs frequently. Neurogenic pulmonary oedema, cardiac dysfunction, and hyponatraemia should be expected in various types of brain injury, including TBI, SAH, seizures, cerebral haemorrhage, and ischaemic stroke. Patients with neurogenic pulmonary oedema after SAH have a higher incidence of symptomatic vasospasm and poorer overall clinical outcome. Stress cardiomyopathy after SAH is also associated with an increased risk of death, poor outcome, and DCI.

There is increasing evidence that, after neurological catastrophes, both sympathetic hyperactivity and a systemic inflammatory response – and especially the interplay between the autonomic and immune system – play important roles in the development of both cardiac and pulmonary pathologies.

CSW is considered the most frequent cause of hyponatraemia in neurological and neurosurgical patients. Although these complications are clinically relevant and associated with adverse outcome, there is still a paucity of evidence on their optimal management.