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Neurogenic pulmonary edema: a current literature review

Edema pulmonar neurogênico: uma revisão atualizada da literatura

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ABSTRACT

Neurogenic pulmonary edema in the setting of critically ill neurologic patients is a condition that is not fully understood, and it is a relatively rare condition. Severe brain damage, such as cerebral and subarachnoid hemorrhage, head injuries and seizures, represents a risk factor for developing neurogenic pulmonary edema. Misdiagnosis and inappropriate management may worsen cerebral damage because of secondary brain injury from hypoxemia or reduced cerebral perfusion pressure. These factors may increase morbidity and mortality. This study aimed to review the current concepts on pathophysiologic mechanisms involved in the development of neurogenic pulmonary edema and discuss the associated clinical and therapeutic aspects.

Keywords: Pulmonary edema; Lung diseases; Respiratory tract diseases

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INTRODUCTION

Clinical and epidemiological aspects

Neurogenic pulmonary edema (NPE) was first described in 1908 in a status epilepticus patient and later in 1928 in a head trauma patient. This condition is poorly understood and diagnosed; its actual incidence is unknown because most of the literature is based on single case reports and necropsy results of a small numbers of patients with no statistical relevance. However, the clinical presentation of NPE is known to range from subclinical to fulminant pulmonary edema. Neurogenic pulmonary edema is related to conditions associated with severe brain injury, such as head trauma,[1,2] subarachnoid hemorrhage,[3] traumatic bulbus injury,[4] intraparenchymal hemorrhage, cerebellar hemorrhage,[5] status epilepticus,[6,7] brain tumor,[8] meningitis,[9] enterovirus 71 encephalitis,[8,10,11] multiple sclerosis,[12,13] ischemic stroke[14] and acute hydrocephalus.[15] Additionally, there are single case reports of pneumocephalus following stereotaxic biopsy,[16] cerebral aneurism embolization,[17] electroconvulsive therapy,[18,19] hanging,[20] acute myelitis[15] and primary spinal cord hemorrhage.[21] Meningeal hemorrhage is the most common cause of neurogenic pulmonary edema.

Classic and fulminant NPE is associated with the more severe brain damage because of massive sympathetic discharge that presents with clinical and radiological pulmonary congestion, pink foam sputum and eventually

death despite appropriate therapy. The patient may have impaired perfusion, tachycardia, dyspnea, tachypnea, reduced oxygen saturation, severe hypertension with transient increased pulmonary capillary pressure and, not rarely, hypotension. Upon cerebral trunk compression or hypoxia, bradycardia and hypertension (i.e., Cushing's reflex) may indicate imminent death. NPE can develop within minutes, hours or days after a causative insult.[22] NPE may cause hemodynamic and respiratory changes because of the excessive adrenergic release, which can normalize within a few days upon cardiovascular normalization. Stunned myocardium syndrome is a condition that may be associated with hypotension, myocardial failure and electrocardiographic and enzyme changes and resembles acute coronary disease. Subclinical NPE may be misdiagnosed as other respiratory conditions, such as pneumonia, embolism, pulmonary contusion and pulmonary congestion because of the excess fluid.[22] Subclinical NPE is closely related to subarachnoid hemorrhage. The proportion of deaths from non-pulmonary causes, such as cardiac, renal, hematological and gastrointestinal causes, is equivalent to the proportion of deaths from neurological causes. The respiratory causes account for 50% of the fatal clinical complications.[23]

For this review, articles on neurogenic pulmonary edema available on Medline and published from January 1997 to September 2011 were selected. A number of references from these articles were also included in this review.

Pathophysiology of neurogenic pulmonary edema

Brain injury, with or without intracranial hypertension and with reduced cerebral perfusion, leads to sympathetic discharge from specific regions. This discharge is primarily from the hypothalamus, bulb and spinal cord and, first, causes NPE by a mechanism related to changes that increase hydrostatic pulmonary pressure (i.e., the blast theory) and, second, occurs because of increased pulmonary capillary permeability (i.e., permeability defect theory).[24-26]

The release of large amounts of catecholamines causes severe systemic vasoconstriction, displaces blood from the systemic to the pulmonary circulation and, consequently, increases the pulmonary blood volume. Concomitantly, reduced left ventricular diastolic and systolic compliance leads to an increased ventricular volume due to either increased venous return or peripheral vascular resistance. This increased volume causes increased end left ventricular filling pressure and left atrial pressure and explains why NPE could be caused by minor peripheral arterial resistance increases and worsened in bradycardia conditions. Both mechanisms (i.e., blood displacement from the systemic to pulmonary circulation and increased left chamber pressure), in combination with intensive pulmonary vasoconstriction, promote increased pulmonary capillary pressure with endothelial injury and fluid leakage to the interstitial region and alveoli. Lymphatic congestion contributes by reducing the ability to drain transudates.[25,26]

Another mechanism involves increased capillary permeability. Sympathetic microvascular stimulation causes micropores to increase in number and size, which allows more fluid into the alveoli. Other mechanisms that increase permeability include neurohumoral factors, such as neuropeptide Y release,[17,27] inflammatory mediators, cytokines, fibrin and fibrin degradation products, the occlusion of the IV ventricle or direct medullary neuron stimulation. The occlusion of pulmonary vessels by microemboli may be a supportive factor for NPE. Platelet count and fibrinogen are reduced following brain insult, which suggests platelet aggregation and microthrombi formation. Platelet aggregation may be a consequence of increased epinephrine concentrations. Plasma thromboplastin levels are increased after head trauma, possibly because of thromboplastin from the brain venous system. Thromboplastin stimulates the extrinsic coagulation cascade and may contribute to the fibrin embolization of pulmonary vessels. Pulmonary intravascular coagulation increases capillary permeability. The release of stress hormones, such as corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), corticosteroids and arginine vasopressin (AVP), are documented in cases of subarachnoid hemorrhage and NPE.[26] Vagotomy in experimental models suggests the involvement of nitric oxide pathways and a role of inducible nitric oxide synthase (iNOS)[28] in the genesis of NPE. Brain injury increases the levels of SB100, a calcium-bound protein, in cerebrospinal fluid and blood. Respiratory tract cells produce and release SB100. These proteins bind to pneumocyte type I receptors, which potentiate inflammatory and immune responses with additional pulmonary damage.[23] Pulmonary endothelial cell apoptosis may have a role in the genesis of NPE.[29]

Neuroanatomical structures related to neurogenic pulmonary edema

Solitary tract nucleus (STN)

STN (bulb) represents glossopharyngeal and vagal afferent terminations from baroreceptors and chemoreceptors. Efferent fibers terminate at the thoracic spinal cord. Injuries to the STN activate alpha-adrenergic

receptors. Thus, damage to the STN could increase pulmonary permeability.[30]

Parvocellular and magnocellular reticular nucleus

These structures are situated between the lower portion of the inferior olivary nucleus and the facial nerve entry (diencephalon) and are related to the Cushing's reflex (i.e., hypertension and bradycardia related to intracranial hypertension). The medullary regions responsible for systemic hypertension are independent of the cardiovagal area that modulates Cushing's bradycardia.

Noradrenergic A1 neurons of caudal ventrolateral medulla

Vasopressin, which is secreted from neuroendocrine cells from supraoptic and paraventricular hypothalamic nuclei, has an inhibitory action. Noradrenergic A1 neural injuries are likely to have a vasopressin-dependent component.[30]

Hypothalamus

Injuries to lateral preoptic hypothalamic areas cause severe visceral vasoconstriction via sympathetic efferent fibers, which displaces blood from systemic to pulmonary circulation. These injuries may contribute less, however, to the genesis of NPE.[30]

Vagal nuclei

A vagotomy in experimental models or injuries to the vagal nuclei cause severe laryngeal and bronchial spasms, which cause airway obstruction and hyperinflation and, consequently, negative pressure in the adjacent non-obstructed areas. This may increase the transcapillary filtration pressure in hyperinflated areas. Conversely, other studies suggest that a vagotomy would cause NPE independent of an adrenergic release, however, with unknown hemodynamic effects.[28,30]

Particularities of neurogenic pulmonary edema in subarachnoid hemorrhage

Muroi et al.[3] prospectively assessed all of the 477 cases of subarachnoid hemorrhage that were admitted to the Zurich University Hospital within the first three days following an ictus, between 1998 and 2005. Severe patients were categorized as those with a clinical Hunt and Hess III-IV score and a radiological Fisher' score between II and IV. The bleeding aneurism location was established via angiography. All patients were treated according to generally accepted protocols. The ambulatory outcomes were assessed after one year using the Glasgow Outcome Scale (GOS). Those patients with an assessment of either GOS 4 (moderately disabled) or GOS 5 (mild or no disability) were rated as having a good outcome. Neurogenic pulmonary edema was retrospectively assessed utilizing clinical criteria, such as pulmonary auscultation, the presence of pink tracheal sputum; aspiration pneumonia or other causes of respiratory failure were precluded. Additionally, the radiological criteria for pulmonary congestion, which was assessed by a radiologist who was blind to the patient's condition, were considered. Clinical and radiological criteria where adhered to. Data from patients with neurogenic pulmonary edema were later retrospectively assessed in relation to pupillary changes, intracranial pressure, electrocardiogram, troponin T and CK-MB by admission. Cardiac index and output were measured using a Swan-Ganz catheter; the catecholamine doses required for hemodynamic stabilization were also measured (dobutamine, dopamine, adrenalin and noradrenaline). Cardiac indexes lower than 3 l/min/m^2 were considered low.

The results showed that NPE occurred in 8% of the cases with subarachnoid hemorrhage. Clinically, patients with NPE had more severe bleeding (Hunt and Hess III - V) compared with patients without NPE. All NPE patients with radiological criteria for severity (Fisher III - IV) had hemorrhages. Of those, 59% of NPE patients died, and only 23% had good neurological outcomes (GOS 4 to 5). The outcomes were worse for patients with NPE compared with patients without neurogenic pulmonary edema. This difference may be explained by the bleeding severity at patient admission. An increased intracranial pressure was observed in 67% of NPE patients. At admission, 33% of patients presenting with NPE had pupillary changes caused by herniation, with a 92% mortality rate. The incidence of NPE caused by posterior circulation aneurism rupture was higher because of the increased intracranial pressure close to the brain bulb.

CK-MB and troponin T changes were found in 61% and 83%, respectively, of NPE patients without a cardiac cause. The troponin levels were approximately 5 times lower than those of acute myocardial infarction patients. The electrocardiographic changes were transient and observed in 33% of the patients (i.e., signs of anterior ischemia and branch block); 33% of the patients had a cardiac index lower than 3 l/kg/m^2. Almost all patients required catecholamine use during the acute phase. However, no patient developed persistent ventricular dysfunction.

Neurogenic stunned myocardium (NSM) syndrome may be associated with NPE. This condition is also commonly related with subarachnoid hemorrhage and, coincidentally, with cerebral vasospasm. NSM is more

common on the third day after bleeding; however, it can manifest at any time within approximately 14 days after an ictus. Left ventricular dysfunction, with eventual bradycardia; changes in QRS, ST, and T waves; and a widened QTc interval may also be present.[31] Electrocardiographic changes are similar to those observed in myocardial ischemia, but without acute coronary disease. Bulsara et al. showed echocardiographic abnormal wall movements, which were more pronounced than anticipated, considering the electrocardiogram findings. This finding would be indicative of stunned myocardium syndrome. Additionally, these authors noted that the CK-MB levels were unable to differentiate this condition from myocardial infarction. However, troponin levels were lower than 2.8 ng/ml, and ejection fractions were lower than 40%, which are consistent with NSM.[32] Different electrocardiographic changes are seen, such as changes to P wave, T wave inversion, ST segment changes, large U waves, Q wave, prolonged QTc interval. Catecholamine release is related to electrocardiographic changes. Prolonged QTc interval is predictive of left ventricular dysfunction.[31,33] Acute pulmonary edema is related to low cardiac output, increased pulmonary capillary pressure and increased pulmonary permeability. Higher Hunt and Hess clinical score levels are associated with a greater likelihood of developing NSM. Cardiac mechanic dysfunction and neurogenic pulmonary edema are transient.[34]

NSM and Takotsubo syndrome coexist in the medical literature and may refer to the same clinical entity. Takotsubo syndrome is related to cardiomyopathy that is induced by emotional stress that includes a massive adrenergic release. Takotsubo syndrome is also known as apical ballooning syndrome or broken heart syndrome and is characterized by transient left ventricular anterior wall dyskinesia and kinetic enhancing of the ventricular base. This condition is unrelated to coronary obstruction. Electrocardiographic changes similar to acute coronary syndrome that include typical chest pain are observed. Patients with neurogenic pulmonary edema have systolic dysfunction and increased cardiac enzymes, which are similar symptoms to those observed in Takotsubo syndrome. However, pulmonary edema is more prevalent in NPE, whereas chest pain and elevation of the ST segment are more frequent in Takotsubo syndrome patients.[35]

Treatment of neurogenic pulmonary edema and neurogenic stunned myocardium

The treatment[3,17,19,36] is primarily based upon hemodynamic and respiratory support, which treats intracranial hypertension and its cause. Mechanical ventilation is recommended to provide appropriate oxygenation. Positive end-expiratory pressure (PEEP) should be judiciously applied because of hemodynamic repercussions that include increased intra-thoracic pressure and, consequently, reduced venous return, which may result in hypotension and worsened cerebral perfusion. Ideally, the patient's hemodynamics should be monitored using a Swan-Ganz catheter or other measures of cardiac output, systemic vascular resistance, pulmonary capillary wedge pressure intracranial pressure measurements and mean blood pressure. Inotropic therapy for neurogenic stunned myocardium includes milrinone and dobutamine. Milrinone is recommended when the systolic blood pressure is above 90 mm Hg, systemic vascular resistance is high or the patient is on chronic beta blockers. Both therapies may be used to increase cardiac output. Dobutamine is preferred if the blood pressure is lower than 90 mm Hg. Milrinone is the preferred treatment for increasing cardiac output for a patient with normal systemic vascular resistance and systolic blood pressure. Dobutamine would be better for increasing the cardiac output in a hypotensive patient with low systemic vascular resistance. Although dobutamine has arrhythmogenic effects, which cause a mild reduction in peripheral resistance, it also increases cerebral perfusion. The use of levosimendan is not supported by clinical experience. Dopamine should not be used in doses greater than 6 mcg/kg/min because the afterload would be increased.

Alpha adrenergic blockers, such as phenoxybenzamine and phentolamine, are not recommended because of the transient condition of the sympathetic release and possible harmful hypotensive effects. These drugs must be used following brain injury but before the adrenergic discharge, and this is difficult to diagnose.

Loop diuretics, such as furosemide, reduce sodium reabsorption and promote arterial and venous dilation, which improves pulmonary congestion and relieves pulmonary circulation. Osmotic diuretics (e.g., mannitol) may reduce intracranial hypertension by reducing the brain edema. These drugs remove intra- and extracellular fluids into the vessels but may precipitate an initial fluid overload.

Opioids cause respiratory depression, relieve anxiety and reduce arterial and venous constriction but make pupillary evaluations difficult because they cause miosis.

The head of the patient's bed should remain elevated by 30º to ease jugular drainage and not worsen intracranial hypertension. Tracheal suctions should be administered as necessary but be short and preceded by appropriate oxygenation. Coughing and the Valsalva reflex increase intra-thoracic and intra-abdominal pressure, which impairs

venous return, therefore, affecting the cardiac output and cerebral perfusion and increasing the intracranial pressure.

Experimental therapeutic reports have suggested a role for mild hypothermia and barbiturate-induced coma.[37] In animal models, isoflurane was suggested to reduce the incidence of NPE.[38,39] Additionally, nitric oxide action on the solitary tract was suggested to reduce NPE. In animal models, interferon-asnt reduced the lung expression of proinflammatory mediators; therefore, this drug could have a therapeutic role.[40] In experimental models, caspase 1 inhibitors were suggested to prevent pulmonary cell apoptosis.[41]

CLOSING REMARKS

NPE and neurogenic stunned myocardium syndrome are urgent medical conditions with poorly identified incidence and not fully understood pathophysiology. The lack of randomized double-blind trials prevents the establishment of evidence-based treatment strategies. This area of intensive medicine clearly demands investigation. NPE is not exclusively an event of mechanical left ventricular overload; it is also related to a systemic inflammatory response and involves complex endocrine, metabolic, immune and hematological phenomena. This complexity renders designing randomized and controlled trials difficult. Finally, professionals treating severely ill neurological patients should promptly identify these conditions and provide appropriate support. This could prevent secondary neurological injuries.

RESUMO

O edema pulmonar neurogênico ainda é um fenômeno pouco compreendido no contexto da assistência ao paciente neurológico grave. Trata-se de uma situação clínica relativamente rara. Situações de importante dano cerebral como hemorragia subaracnóidea, traumatismos encefálicos severos, hemorragias cerebrais intra-parenquimatosas, crises convulsivas ou outras condições específicas fazem o perfil do paciente com risco de desenvolver edema pulmonar neurogênico. A falta de reconhecimento desta condição e o seu inadequado manuseio podem levar à piora do sofrimento cerebral por adicional lesão cerebral secundária em decorrência de hipoxemia e de redução da pressão de perfusão cerebral com aumento da morbidade e da letalidade. O objetivo desta revisão foi o de levantar aspectos atuais da fisiopatologia do edema pulmonar neurogênico, sua importância clínica e terapêutica. Embora de ocorrência relativamente rara, o edema pulmonar neurogênico deve ser prontamente reconhecido e tratado para que se evite dano cerebral secundário adicional. Apesar de ainda não totalmente elucidado, o conhecimento da base da fisiopatologia tem importância na estratégia do seu manuseio. Deve-se ter em mente a identificação de diagnósticos diferenciais como pneumonia aspirativa, embolia pulmonar, contusão pulmonar, congestão por sobrecarga de volume dentre outras situações. De forma semelhante, devem ser consideradas situações correlatas como a síndrome do miocárdio atordoado ("stunned myocardium") que podem estar presentes ou associadas ao edema pulmonar neurogênico.

Descritores: Edema pulmonar; Pneumopatias; Doenças respiratórias

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