NEUROGENIC PULMONARY EDEMA

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SUMMARY – The association of pulmonary edema with central nervous system disease without underlying cardiopulmonary disease is known as neurogenic pulmonary edema (NPE). The most common precipitants of NPE are epileptic seizures, head injury, and subarachnoid or intracerebral hemorrhage. Since the most common neurologic events are associated with increased intracranial pressure, intracranial hypertension is considered to be a key etiologic factor. Various theories regarding the pathogenesis of NPE have been focused on the potential roles for the hypothalamus, the medulla, elevated intracranial pressure, and activation of the sympathoadrenal system. A distinctive form of myocardial injury, contraction band necrosis, is the likely pathologic substrate of cardiac injury. NPE characteristically presents within minutes to hours of a severe central nervous system insult. Resolution of NPE usually occurs within several days. Dyspnea is the most common NPE associated symptom, and mild hemoptysis is also present in many patients. Definitive diagnosis of NPE is difficult because of the nonspecific nature of the clinical signs and routine diagnostic tests. The outcome of patients with NPE is usually determined by the course of the neurologic insult that has produced NPE, and specific treatment should focus on the underlying disorder. NPE is generally managed in a supportive and conservative fashion because many cases of NPE are well tolerated and the majority of them resolve within 48 to 72 hours.

Key words: Lung – physiopathology; Lung diseases – physiopathology; Pulmonary edema – physiopathology; Pulmonary edema – etiology; Pulmonary edema – diagnosis; Brain diseases – complications

Introduction – Definition

The association of pulmonary edema with central nervous system (CNS) disease without underlying cardiopulmonary disease is known as neurogenic pulmonary edema (NPE). NPE, a relatively rare form of pulmonary edema, represents an increase in pulmonary interstitial and alveolar fluid due to, and usually developing rapidly after, acute, well defined damage to the CNS. This entity is frequently classified as a form of the acute respiratory distress syndrome (ARDS), although its pathophysiology and prognosis are significantly different.

Moutier was the first to report on the association between CNS injury and pulmonary edema in 1918[1]. He observed the frequent occurrence of fatal acute pulmonary edema after cerebral trauma from war injuries. Since then, NPE has been reported in a wide variety of CNS injuries.

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Etiology

The etiologic causes of NPE are presented in Table 1.

Epileptic seizures are the most common precipitant of NPE. Edema generally occurs in the postictal period, and may occur repeatedly in a given individual[2-4]. Up to one-third of patients with fatal status epilepticus have evidence of NPE in several older series[5,6], and pulmonary edema was observed in 45 of 52 patients in an autopsy series of patients with epilepsy and unexplained sudden death[7]. In recent studies NPE has also been proposed to be one of the mechanisms for sudden unexpected death in epilepsy (SUDEP), suggesting that the incidence of SUDEP increases with the severity of epilepsy in the study population, duration of epilepsy, number of tonic-clonic seizures, mental retardation and simultaneous treatment

Table 1. Etiology of neurogenic pulmonary edema

Major causes	Minor causes
• Epileptic seizures	• Guilllain-Barré syndrome
• Head injury	• Multiple sclerosis with medullary involvement
• Cerebral hemorrhage	• Nonhemorrhagic stroke
	• Bulbar poliomyelitis
	• Air embolism
	• Brain tumor
	• Electroconvulsive therapy
	• Bacterial meningitis
	• Cervical spine cord injury
	• Trigeminal nerve blockade
	• Vertebral artery ligature
	• Spinal cord AV malformation rupture
	• Induced general anesthesia
	• Colloidal cyst
	• Hydrocephalus
	• Reye's syndrome

with more than two antiepileptic drugs[8]. It is still unclear from these and other series whether NPE was the proximate cause of death. However, the importance of awareness of NPE association with epileptic seizures needs to be emphasized[9].

Blunt or penetrating ***head injury***, including neurosurgical procedures, is a well known cause of NPE[2,10]. NPE usually occurs in association with elevated intracranial pressure (ICP) but raised ICP is not a necessary precondition for NPE[11]. Impaired pulmonary function is a frequent yet poorly understood complication of acute head injury. It is hypothesized that NPE would occur early after head injury and that it would have a continuum of clinical severity depending on the severity of head injury and associated intracranial hypertension. The incidence of NPE in isolated head injury patients dying at the scene was found to be 32%, and in patients with isolated head injury dying within 96 hours 50% in a study using a large autopsy database and inpatient head injury data base to search for cases of NPE. It is concluded that the process of edema formation begins early in the clinical course and is isolated to the lung[12].

NPE commonly complicates ***subarachnoid*** or ***intracerebral hemorrhage***. It may frequently develop several days after a hemorrhage and recur after apparent initial resolution[13]. As an example, one series of 78 fatal causes of subarachnoid hemorrhage (SAH) found pathologic evidence of pulmonary edema in 71% of cases; ante mortem clinical evidence of pulmonary edema was present in 31% of patients[14]. Another study reviewed the records of patients with acute SAH treated during seven years, analyzed 300 patients, and found that 2% of patients experienced NPE[15]. Since SAH patients often exhibit specific myocardial lesions and NPE, there is an argument for all SAH patients to have echocardiography and continuous monitoring of respiratory rate, pulse oximetry, blood pressure and electrocardiogram, to optimize cardiorespiratory function and allow for subsequent definitive management of SAH[16].

Prevalence

In the USA, up to one-third of patients with status epilepticus have evidence of NPE[5-7]. In more than a half of patients, severe blunt or penetrating head injury is associated with NPE[12]. Seventy-one percent of fatal SAH cases were complicated by NPE[14]. NPE may complicate subarachnoid and intracerebral hemorrhage in 30% to 70% of patients, and may recur after initial resolution[15].

Pathophysiology

Although NPE has been recognized for more than a century, its pathophysiologic mechanisms remain incompletely understood. Since the most common neurologic events are associated with increased ICP, intracranial hypertension is considered to be a key etiologic factor. Generally, NPE is regarded as a noncardiogenic event. The consistent finding of high protein-content edema fluid and normal wedge pressures supports this view.

Neuroanatomic structures

The identities of neurologic structures that are critical for the formation of NPE are more completely appreciated than the mechanism by which lesions in these areas produce NPE. Baker's description dating from 1957 is particularly interesting[17]. In his study of NPE following poliomyelitis, Baker noted that only patients with pathologic changes in the region of dorsal nucleus of the vagus and medial reticular nuclei of the medulla developed NPE. Various theories regarding the pathogenesis of NPE have centered on the potential roles for the hypothalamus, the medulla, elevated ICP and activation of the sympathoadrenal system[17-29]. Both hypothalamic lesions and stimulation of the vasomotor centers of the medulla can increase output along the sympathetic trunk. At present, medulla

oblongata is believed to be the critical anatomic structure involved in the pathogenesis of NPE, probably acting *via* the sympathetic component of the autonomic nervous system. Experimental evidence supporting this theory includes the following[20,21]:

- Bilateral lesions of one of the nuclei in the medulla, the nucleus of the solitary tract, produce profound pulmonary and systemic hypertension as well as pulmonary edema.
- Lesions in the A1 noradrenergic neurons in the ventrolateral medulla can also lead to systemic hypertension and to NPE.
- Alpha-adrenergic blockade (e.g., with phentolamine) is able to abolish the formation of NPE, suggesting an important role for sympathetic activation[23-25]. Similarly, NPE can be prevented by spinal cord transsection at or above the C7 level, below which sympathetic fibers leave the lateral part of the cord to form the paraspinal sympathetic trunks, and it can be prevented by denervation of the lungs by section of the splanchnic sympathetic fibers to the lungs. Also, NPE may be produced by stimulation of the cord at the C7-C8 level with the cord and sympathetic nerves intact.

Possibly, acute neurologic crisis accompanied by marked increase in ICP stimulates the hypothalamus and the vasomotor centers of the medulla. This in turn initiates a massive autonomic discharge mediated by preganglionic centers within cervical spine. Catecholamines, released in massive quantities due to hypothalamic stress from SAH result in specific myocardial lesions and hydrostatic pressure injury to the pulmonary capillaries causing NPE[16]. Despite the fact that the damage to the hypothalamus owing to serious intracranial organic disease may cause NPE, radiographic investigation of the hypothalamus by computed tomography is rarely performed. A recent study presented 22 consecutive patients suffering from NPE caused by serious intracranial organic disease and investigated the relationship between NPE and abnormal radiographic findings of the hypothalamus. In 11 cases organic lesions were noted in the hypothalamus, and ten (91%) of these patients died from NPE. In contrast, of the remaining 11 cases without significant radiographic findings of organic lesions in the hypothalamus, only two two (18.2%) patients were lost. It was concluded that hypothalamic damage was not always found by radiography in patients with NPE due to critical intracranial diseases, but once abnormal findings in the hypothalamus of these patients were noted, their prognosis would become significantly poor[31].

Mechanisms of edema formation

NPE requires that a central nervous system event produce a dramatic change in the Starling's forces, which govern the movement of fluid between the capillaries and the pulmonary interstitium and/or increase the permeability of pulmonary capillaries.

Changes in capillary hydrostatic pressure

Because it is unlikely that a central nervous system event could rapidly change capillary or interstitial oncotic pressure, interstitial hydrostatic pressure or lung lymph flow alterations in pulmonary vascular pressures appear to be the most likely Starling's force to influence the formation of NPE[2]. This hypothesis is supported by observations in which early analysis of NPE fluid revealed a low fluid to serum protein ratio consistent with hydrostatic edema[32].

Several experimental observations suggest mechanisms by which pulmonary capillary hydrostatic pressure could be acutely increased:

- Left ventricular performance may deteriorate secondarily to excessive venous return to the heart, systemic hypertension and negative inotropic influences of excessive vagal tone, and may produce passive elevation of left atrial and pulmonary capillary pressures[33-38]. However, NPE in humans and animal models is well described in the absence of left atrial or systemic hypertension, and elevations of pulmonary capillary wedge pressure, which are observed often, appear inadequate to produce NPE[39].
- Pulmonary vasoconstriction can occur with intracranial hypertension or sympathetic stimulation, and can elevate capillary hydrostatic pressure and produce pulmonary edema without affecting left atrial, systemic or pulmonary capillary wedge pressures[23,39].

Changes in pulmonary capillary permeability

The above analysis of Starling's forces assumes constant vascular permeability. An increase in capillary permeability could result in NPE without requiring an increase in pulmonary capillary hydrostatic pressure. Suspicion that increased pulmonary capillary permeability may play a role in NPE is based largely upon the description of protein-rich edema fluid in some patients and experimental models, and the inability to consistently demonstrate causative hemodynamic alterations among patients with NPE[32,40,41].

The mechanisms by which neural influences could produce changes in pulmonary vascular permeability have not been well defined. Several possibilities have been suggested:

- Because alpha adrenergic blockade can protect against NPE and sympathetic stimulation can produce it, it has been suggested that epinephrine or norepinephrine may directly increase vascular permeability. However, direct infusion of these substances into the pulmonary circulation does not produce such an effect[42].
- Alpha-adrenergic agonists released in response to brain injury could cause the release of a second mediator, which increases vascular permeability (e.g., endorphins, histamine, bradykinin)[2].
- An initial rapid increase in pulmonary vascular pressure (e.g., due to pulmonary vasospasm and increased systemic venous return) could cause pulmonary microvascular injury with a subsequent increase in permeability[43]. This "blast theory", as proposed by Theodore and Robin, suggests that NPE results primarily from an insult to the pulmonary circulation. It is supported by findings in rabbits that pulmonary capillaries are damaged when pressures exceed 40 mm Hg[44], and may explain the frequent observation of mild hemoptysis or pulmonary hemorrhages in patients with NPE[10]. However, the rapid development of acute pulmonary hypertension is not a necessary precondition for the development of NPE. Elevated pulmonary vascular pressures in the context of neurologic injury do not invariably lead to NPE either[45].

Pathology

A distinctive form of myocardial injury, contraction band necrosis (myofibrillar degeneration or coagulative myocytolysis) is the likely pathologic substrate of cardiac injury[38].

Mort ality and Morbidity

The mortality rates following NPE have not been well documented in the literature. The outcome is usually determined by the course of the neurologic insult that has produced NPE.

Clinical Presentation

NPE characteristically presents within minutes to hours of a severe central nervous system insult. Resolution of NPE usually occurs within several days. Dyspnea is the most common associated symptom and mild hemoptysis is also present in many patients[46]. Physical examination generally reveals tachypnea, tachycardia and basilar rales that are consistent with pulmonary edema (Table 2).

Laboratory studies are nonspecific and therefore not helpful in making a diagnosis.

Chest x-rays typically show a normal size heart with evidence of bilateral alveolar filling, but may also mimic congestive heart failure with cephalization of blood flow[47].

Hemodynamic measurements with right heart catheterization, such as blood pressure, cardiac output and pulmonary capillary wedge pressure (i.e. Swan-Ganz catheterization) are necessary to differentiate NPE from hydrostatic or cardiogenic pulmonary edema and usually are normal by the time NPE is diagnosed[46].

These findings may be confused with aspiration pneumonitis. Reliable differentiation of these two syndromes is difficult because they both commonly occur in settings of altered consciousness, such as postictal states. NPE tends to develop more rapidly than aspiration pneumonia, and the presence of fever and more focal infiltrates favors infection. A key retrospective distinction is that NPE will typically resolve within hours to several days, while aspiration pneumonitis may take one to two weeks for resolution. Other causes of pulmonary edema such as congestive heart failure and acute respiratory distress syndrome must also be excluded[48,49].

Definitive diagnosis of NPE is difficult because of the nonspecific nature of clinical signs and routine diagnostic tests. The clinical diagnosis of NPE is based largely upon the occurrence of pulmonary edema in the appropriate setting and in the absence of another obvious cause. There may be a broad range of severity of NPE so that many mild cases are never detected. NPE can produce fulminant edema and contribute to death, but mortality is more commonly due to the underlying neurologic disease.

Treatment

The outcome of patients with NPE is usually determined by the course of the neurologic insult that has produced NPE, and specific treatment should focus on the

Table 2. Physical findings in neurogenic pulmonary edema

• Tachypnea
• Tachycardia
• Bibasilar crackles
• Respiratory distress
• Pulmonary edema – with normal jugular venous pressure and absence of cardiac gallop
• Fever – may occur secondarily to neurologic disturbance

underlying disorder. NPE is generally managed in a supportive and conservative fashion because many cases of NPE are well tolerated and the majority of them resolve within 48 to 72 hours.

General supportive measures

Supplemental oxygen may be required and mechanical ventilation may be necessary in some circumstances, either noninvasive by face mask or endotracheal tube. Positive pressure ventilation, particularly when high levels of positive end expiratory pressure are used, should be employed cautiously because it can reduce cerebral venous return and worsen intracranial hypertension[46,48]. Maintenance of low cardiac filling pressures may decrease edemagenesis, but care must be taken to avoid compromise of cardiac output and cerebral perfusion. Pulmonary artery catheterization may be helpful in guiding therapy[49].

Pharmacotherapy

Pharmacologic agents are not used routinely in the treatment of NPE. Some authors advocate several agents, but assessment of their efficacy is difficult because NPE is usually a self-limited condition that ameliorates spontaneously.

- Alpha adrenergic antagonists – numerous experimental models of NPE have shown that alpha-adrenergic blockers (e.g., phentolamine) can prevent or hasten the resolution of NPE[50-52]. No human clinical trials have firmly established the safety and efficacy of these agents in NPE, but they are often used in this setting, particularly if systemic hypertension is present. Care must be taken to avoid precipitating systemic hypertension, which can diminish cerebral perfusion.
- Other agents – a variety of medications have been used to treat patients with NPE, but assessment of their efficacy is difficult because of the small number of patients treated, the nonrandomized nature of the reports, and the fact that NPE is usually a self-limited condition in the absence of treatment. Agents which have been advocated include:
  - beta-adrenergic antagonists – increase lymph flow and edema in sheep and reduce histamine-induced augmentation of pulmonary vascular permeability[2;]
  - dobutamine – may increase cardiac output, decrease pulmonary capillary wedge pressure and promote diuresis[53,54]; and
  - chlorpromazine – may act *via* blockade of alpha-adrenergic receptors or by as yet undefined mechanisms[55].

Further Inpatient Care

These patients are usually admitted to the hospital. Intensive care admission may be required if the patient develops worsening hypoxemia or respiratory distress.

Prognosis

- NPE is usually well tolerated by the patient and the process generally resolves within 48 to 72 hours.
- Prognosis is determined by the course of the underlying neurologic problems.

Neurogenic pulmonary edema is an underdiagnosed clinical entity. Its pathophysiology is multifactorial but largely unknown. Physicians should consider NPE when neurologic patients suddenly become dyspneic. The mortality rate is high, but surviving patients usually recover very quickly.

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Sažetak

NEUROGENI PLUĆNI EDEM

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Neurogeni plućni edem je rijedak oblik plućnog edema obilježen povišenjem plućne intersticijske i alveolarne tekućine, a razvija se unutar nekoliko sati od nastanka dobro definiranog neurološkog oštećenja. Najčešći uzroci neurogenog plućnog edema su epileptični napadaji, ozljede glave i subarahnoidna ili intracerebralna krvarenja. Kako su najčešći neurološki poremećaji povezani s povišenim intrakranijskim tlakom, smatra se da je povišeni intrakranijski tlak ključni čimbenik u nastanku neurogenog plućnog edema. Različite teorije o patogenezi neurogenog plućnog edema smatraju da u njegovom nastanku moguću ulogu imaju hipotalamus, medula oblongata, povišen intrakranijski tlak i aktiviranje simpatoadrenergičnog sustava. Neurogeni plućni edem znakovito nastupa unutar nekoliko minuta do sati od nastanka teškog oštećenja središnjeg živčanog sustava. Najčešće se očituje naglim nastankom dispneje, a ponekad se javlja i blaga hemoptiza. Zbog njihove nespecifičnosti laboratorijske pretrage ne pomažu u donošenju dijagnoze neurogenog plućnog edema. Ishod u bolesnika s neurogenim plućnim edemom obično određuje tijek osnovne neurološke bolesti koja je i dovela do tog stanja, pa specifično liječenje treba usmjeriti na liječenje osnovne bolesti. Neurogeni plućni edem se općenito zbrinjava konzervativnom potpornom terapijom, jer bolesnici u većini slučajeva ovo stanje podnose relativno dobro i u većini slučajeva simptomi prestaju unutar 48-72 sata.

Ključne riječi: Pluća – fiziopatologija; Plućne bolesti – fiziopatologija; Plućni edem – fiziopatologija; Plućni edem – etiologija; Plućni edem – dijagnostika; Bolesti mozga – komplikacije