Neurological Perspectives of Neurogenic Pulmonary Edema

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Keywords

Pulmonary edema · Cerebral · Brain-lung disease · Stress · Sympathetic overstimulation

Abstract

Background: Neurogenic pulmonary edema (NPE) is characterized by acute respiratory distress triggered by acute, severe compromise of the central nervous system (CNS). This review aims at summarizing and discussing recent and previous findings about the type and frequency of CNS triggers of NPE, pathogenesis, diagnosis, treatment, and outcome of patients experiencing NPE. **Key Messages:** NPE is diagnosed in the presence of pink, frothy sputum, pulmonary edema, bilateral opacities on X-ray, $\text{PaO}_2:\text{PiO}_2 < 200$ mm Hg, acute CNS compromise with increased intra-cranial pressure, rapid resolution within 48–72 h, and the absence of alternative causes of respiratory distress. The most common cerebral triggers of NPE include enterovirus-71-associated brainstem encephalitis, subarachnoid bleeding, intracerebral bleeding, traumatic brain injury, epilepsy, ischemic stroke, intracranial/spinal surgery, multiple sclerosis, electroconvulsive therapy, subdural/epidural hematoma, intoxication, hypoxia, and hydrocephalus. Simultaneous treatment of CNS and

pulmonary compromise is required. Cerebral treatment involves infectiologists, neurologists, and neurosurgeons. Pulmonary treatment is mainly supportive, but if ineffective, extracorporeal membrane oxygenation or thermodilution are alternative options. Applying intensive care measures, the outcome of NPE has improved. **Summary:** CNS-disease triggering NPE is more variegated than anticipated. Delineation of NPE from other pulmonary or cardiac conditions mimicking NPE is crucial to take appropriate measures and improve the outcome of these patients.

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Introduction

Neurogenic pulmonary edema (NPE) is defined as acute respiratory distress triggered by severe stress from acute compromise in the central nervous system (CNS), most frequently in the brainstem or the hypothalamus [1, 2]. According to the 2012 Berlin definition [3], NPE is a form of acute respiratory distress syndrome, characterized by marked, acute-onset, extra-vascular accumulation of interstitial pulmonary fluid [1]. An acute-onset (<4 h (usually 30–60 min after the CNS event) and a delayed

onset (12–72 h after the CNS event) form are delineated [4]. NPE is more prevalent in females compared to males [5]. NPE resolves within 72 h in >50% of the patients [5]. NPE was first described by Shanahan in 1908 [1]. NPE is diagnosed by clinical examination, X-ray of the lungs, and exclusion of any primary pulmonary or cardiac lesion [1]. This review aims at summarizing and discussing previous and novel findings about type and frequency of cerebral triggers of NPE, pathogenesis, diagnosis, treatment, and outcome of patients experiencing NPE.

Methods

Data for this review were identified by searches of MEDLINE for references of relevant articles. Search terms used for screening the database were “neurogenic pulmonary edema,” “Takotsubo syndrome,” or “stunned myocardium” in combination with “cerebral,” “brain,” “encephalopathy,” “epilepsy,” “seizure,” “subarachnoid bleeding,” “intracerebral bleeding,” “stroke,” “meningitis,” “encephalitis,” “traumatic brain injury,” “head injury,” and “headache.” Inclusion criteria that search results had to meet were: original study, publication in English, and investigation of humans. Exclusion criteria applied were as follows: article language other than English, review, editorial, letter, or comment, or animal study. Only original articles published between 1966 and 2019 were included. Reference lists of retrieved studies were checked for references of studies not directly identified by the PubMed search. Review articles were cited only when providing a comprehensive overview of a specific topic.

Results

Clinical Presentation of NPE

NPE manifests clinically with dyspnea, tachypnea, tachycardia, cyanosis, and rales, crackles, or rhonchi [6]. Blood tests may reveal hypoxemia (low PaO₂), a PaO₂/PiO₂ ratio <200, and mild leukocytosis [2]. Chest X-ray usually shows bilateral alveolar opacities without cardiomegaly (pulmonary edema) with diffuse bilateral alveolar infiltrates [7]. The acute as well as the delayed onset form usually resolve within 48–72 h after onset [2]. Concerning the delayed onset form, >90% of the cases present with bilateral diffuse infiltrates [5]. Since NPE may be accompanied by cardiac damage [8], differentiation between pulmonary and cardiac pulmonary edema may not be easy in each case.

Pathogenesis of NPE

Despite extensive ongoing research, the pathogenesis of NPE is poorly understood [1]. The most frequently promoted theory about the pathophysiological mecha-

nism leading to NPE suggests that sympathetic overstimulation (catecholamine storm) leads to generalized vasoconstriction [9]. Systemic vasoconstriction is assumed to pool blood from the systemic circulation to the pulmonary circulation resulting in increased pulmonary hypertension and increased pulmonary capillary hydrostatic pressure [9]. Additionally, pulmonary blood is displaced into low pressure areas [2, 10, 11]. The increase in hydrostatic and Starling forces after a CNS lesion mediates damage of the capillary endothelium, resulting in leakage of intravascular, protein-rich fluid to the alveolar space and to the interstitial pulmonary spaces leading to hypoxxygenation (“blast-theory”) [1, 12]. Increase in hydrostatic pressure and permeability may, however, most likely occur through separate mechanisms.

Elevation of systemic hypertension and increase in left atrial and pulmonary hydrostatic pressure, culminating in pulmonary edema, are attributed to surges of sympathetic, particularly alpha-adrenergic activity as the initial event induced by lesions of the hypothalamus or the medulla [2, 6, 13]. Sympathetic overactivity is assumed to originate from trigger zones, being activated by the sudden increase of the intra-cranial pressure or decrease of the cerebral blood flow. An argument in favor of predominant affection of the sympathetic system is that stellate gangliotomy but not bilateral vagotomy prevents NPE in mice [14, 15]. A further argument is that NPE cannot develop in a denervated lung [16]. Increased permeability of pulmonary capillaries can be attributed to stimulation of alpha- or beta-adrenergic receptors by sympathetic overactivity [2, 9, 13, 17]. An argument in favor of this hypothesis is that systolic dysfunction in some patients with NPE may be due to alpha-adrenergic effects resulting in increased venous return and pulmonary venous constriction with consecutive increase in hydrostatic pressures and lung edema. There are also indications that high intracapillary pressure may damage pulmonary capillaries [18]. Another mechanism to explain increased pulmonary capillary permeability is the release of cytokines from the triggering cerebral lesion [19].

Types of Triggers of NPE

Since the first description of NPE, a number of different CNS triggers has been identified, which were made responsible for the development of NPE. These include enterovirus (EV)-71-induced brainstem encephalitis [20], subarachnoid bleeding (SAB) [21], intracerebral bleeding (ICB) [22], traumatic brain injury (TBI) [23], ischemic stroke [24], epilepsy [25], subdural hematoma [26], epidural hematoma [27], cerebral or spinal surgery [28], ce-

rebral mass lesion [29], or other rarer causes (Table 1). According to a study of 36 patients with SAB-triggered NPE, predictors for the occurrence of NPE in patients with SAB were World Federation of Neurological Surgeons class, total power, and normalized low-frequency component [30]. When evaluating ECGs of these patients, it turned out that ECG predictors of NPE were abnormal Q- and QS-wave and nonspecific ST- or T-wave changes [31].

Frequency of Triggers of NPE

There are no systematic, prospective studies about the frequency of triggers of NPE available, but according to retrospective studies, the most frequent CNS disorders causing NPE include EV-71-associated brainstem encephalitis (myelitis), SAB (>50% of cases) [1], open or closed TBI, and epilepsy with generalized seizures or epileptic states [1, 4]. When screening the literature about NPE for CNS triggers between 2012 and 2019 (last 6 years), the trigger was EV-71-associated brainstem encephalitis in 621 cases, SAB in 97 cases, ICB in 34 cases, TBI in 32 cases, and seizure in 8 cases (Table 1). Most data about the prevalence of NPE originate from studies of patients with SAB. Prevalence figures from the different studies, however, are highly variable. In a study of 78 patients experiencing fatal SAB, the rate of NPE diagnosed upon clinical features, was 31% [32]. After combining these figures with autopsy data of the 78 patients, the rate of NPE increased to 78% [32]. In another study of 70 patients with SAB, 16% had experienced fulminant NPE [33]. A low prevalence of NPE was detected in a study of 234 patients with SAB of which only 16 (7%) developed NPE [34]. In a retrospective analysis of 686 fatalities from TBI or CNS bleeding, the prevalence of NPE was 51% [17]. In brain-dead organ donors, the prevalence of pulmonary edema, of which the majority presumably reflects NPE, was reported as 13–18% [35]. In a study of 63 SAB patients, 7 (11%) had also developed NPE [34].

NPE and Takotsubo Syndrome

Takotsubo syndrome (TTS) is defined as acute-onset heart failure after exorbitant stress from an endogenous or exogenous burden [36]. Echocardiographically, TTS is characterized by hypokinesia, dyskinesia, or akinesia of a left ventricular myocardial area not confined to the territory of a coronary artery [36]. Four types of TTS are delineated, the apical type, which is the most common, the midventricular type, the basal type, and the global type, which has the worst prognosis [37]. Several cases have been reported in which TTS was accompanied by NPE due to the same trigger (Table 2). The largest study in-

cludes 234 patients with SAB of whom 14 had NPE and TTS at the same time [34]. However, it can be assumed that many cases have been missed due to the interpretation of lung edema as cardiogenic following heart failure from TTS. Additionally, several cases with TTS and lung edema have been reported without specifying if lung edema fulfilled the diagnostic criteria for NPE or not [38–40]. Arguments for a common pathophysiology are that the triggers can be the same and that the frequency of cerebral triggers is similar. Another argument for a common trigger is the study of Inamasu et al. [34] in which 14 patients with NPE after SAB also had TTS.

Diagnosis

NPE is diagnosed upon clinical presentation, with a chest X-ray, and after exclusion of various differential diagnoses [4]. NPE is frequently diagnosed at the time of postmortem at autopsy, particularly in patients who die from sudden unexplained death in epilepsy (SUDEP) or in patients with TBI [1]. Proposed criteria for diagnosing NPE include pulmonary edema, bilateral opacities (infiltrates) on X-ray of the lungs, rapid resolution of the opacities, pink, frothy sputum or occasionally hemoptysis, $\text{PaO}_2:\text{PiO}_2 < 200$ mm Hg, acute CNS compromise severe enough to increase the intra-cranial pressure, absence of left atrial hypertension on echocardiography, and absence of other common causes of respiratory distress or acute respiratory distress syndrome. Differential diagnoses of NPE that have to be excluded before diagnosing NPE include cardiogenic pulmonary edema, aspiration pneumonia, pneumonitis, sepsis, negative pressure pulmonary edema, post-airway obstruction edema, ventilator-associated pneumonia, ventilation-induced lung injury, and transfusion-related lung injury [1, 2, 4, 13]. If heart failure was excluded and if pulmonary edema develops rapidly and bilaterally, and without a definite cause, NPE is quite likely [4]. If clinical or radiological abnormalities resolve within 48–72 h after onset, NPE should be strongly suspected [4].

Treatment

Conventional Strategies

Generally, treatment of NPE is based on interventions on the neurological side and on measures to resolve pulmonary edema. Cerebral treatment is the domain of infectiologists, neurologists, and neurosurgeons. Treatment of lung edema is the domain of critical care specialists and pulmologists. Treatment of NPE is mainly supportive, including vasoactive compounds, diuretics, fluid supplementation, supplemental oxygen, mechanical

Table 1. Type and frequency of NPE triggers reported during the last 6 years

CNS trigger	NOP	Reference
Infectious diseases		
HFMD (enterovirus-71 brainstem encephalitis)	557	[51]
HFMD (enterovirus-71 brainstem encephalitis)	35	[52]
HFMD (enterovirus-71 brainstem encephalitis)	18	[53]
Aseptic meningitis (endothelin-1 ↑)	10	[54]
Cryptococcal meningoencephalitis	1	[55]
Cerebral bleeding		
SAB	36	[21]
ICB	30	[22]
SAB	20	[56]
SAB	17	[57]
SAB	16	[58]
SAB	8	[43, 48, 59, 60]
ICB (medulla)	2	[61]
ICB	1	[26]
Cerebellar hemorrhage	1	[41]
Epidural hematoma	1	[27, 62, 63]
Subdural hematoma	1	[26]
Acute subdural hematoma during spinal surgery	1	[64]
Spinal AVM rupture	1	[65]
Rupture of AVM	1	[66]
Traumatic brain injury (open or closed)		
TBI	25	[23]
TBI	3	[49, 67, 68]
Cervical medullary trauma	1	[1]
Road traffic accident	1	[69]
Posterior fossa extradural hematoma	1	[70]
Gunshot in the head (transplant donor)	1	[47]
Epilepsy		
Single seizure	3	[4, 21, 71, 72]
Febrile seizures	2	[73, 74]
Seizure during HBOT	1	[25]
Focal/bilateral tonic-clonic seizures	1	[75]
Seizure during pregnancy	1	[76]
Ischemic stroke		
Vertebral artery dissection	2	[24, 77]
Left lateral medulla	1	[78]
MCAD stroke, thrombolysis	1	[79]
Bilateral ischemic stroke	1	[80]
Brainstem	1	[81]
Cerebellar stroke after snake bite	1	[82]
Head surgery		
Carotid endarterectomy	1	[28]
Posterior cranial fossa surgery	1	[42]
Cerebral mass lesion		
Meningeoma	1	[83]
Medullary hemangioblastoma	1	[29]
Immunological		
Multiple sclerosis	12	[84]
Multiple sclerosis	1	[85]
Other		
Acute obstructive hydrocephalus	2	[86, 87]
Electro-convulsive therapy	2	[88, 89]
Hypoxic-ischemic brain injury	1	[46]
Amphetamine (cerebral edema)	1	[45]
Coil embolization of an aneurysm	1	[90]

NOP, number of patients; HBOT, hyperbaric oxygen therapy; CNS, central nervous system; SAB, subarachnoid bleeding; ICB, intracerebral bleeding; TBI, traumatic brain injury; MCAD, right median cerebral artery; AVM, arterio-venous malformation; HFMD, hand foot mouth disease; SDH, subdural hematoma.

Table 2. Cases in which NPE was associated with TTS

Type of TTS	NOP	Trigger	Reference
Apical	1	Carotid endarterectomy	[77]
Apical	1	Meningeoma	[83]
Apical	1	Rupture of AVM	[64]
Apical	1	Multiple sclerosis	[91]
Apical	1	SAB	[92]
Apical	1	SAB	[27]
Apical	1	Medullar hemangioblastoma	[29]
Ns	16	SAB	[34]

In large series of TTS due to SAB, however, NPE has not been described [93, 94].

NOP, number of patients; ns, not specified; NPE, neurogenic pulmonary edema; AVM, arterio-venous malformation; SAB, subarachnoid bleeding; TTS, Takotsubo syndrome.

ventilation if necessary, and control of pulmonary vascular pressures. Fluid supplementation is challenging, as high volumes may be necessary for cerebral rescue, whereas the management of lung edema requires volume restriction [2]. Ultrasound of the lungs may guide the intensivist with regard to the amount of volume substitution [41, 42]. High positive, end-expiratory pressure together with dobutamine and norepinephrine may be necessary to stabilize pulmonary compromise [43]. There are indications from animal studies that angiotensin-converting enzyme inhibitors may have a beneficial effect in patients with NPE [44]. Since steroids may be beneficial for certain neurological conditions, such as multiple sclerosis or mass lesions with concomitant edema, and harmful in other conditions, such as TBI, application of steroids in NPE patients must be individualized [2]. In a recent study of 22 children with EV-71-induced brainstem encephalitis and NPE, the administration of milrinone resulted in a significantly better outcome with lower 1-week mortality than in controls receiving conventional treatment [20].

Strategies for Nonresponsive NPE

If NPE is nonresponsive to conventional or salvage therapies, the initiation of extracorporeal membrane oxygenation (ECMO) can be an effective alternative, leading to rapid normalization of oxygenation parameters [45]. ECMO has been successfully applied in a 20-year-old female with cerebral edema due to amphetamine intoxication and NPE [45]. ECMO has also been applied in a patient with NPE due to cerebral hypoxia during cardio-pulmonary resuscitation [46]. ECMO was even beneficial in a recipient of a lung from a donor experiencing NPE [47]. ECMO has also been applied in a 28-year-old female with NPE following an SAB [48]. Nonetheless, the outcome of

this particular patient was fatal [46]. ECMO may be beneficial in patients with NPE due to TBI, although ECMO is generally contraindicated in neurological conditions such as TBI or CNS disorders that are likely to require surgical intervention [48]. The transpulmonary thermodilution indicator technique is another therapeutic option for nonresponsive NPE [49]. The method relies on the injection of a cold saline bolus into the central venous circulation, subsequent measurement of changes in the blood temperature, and calculation of thermodilution curve [41]. Various parameters calculated from this curve can help to distinguish between hydrostatic NPE and NPE due to increased permeability, and thus optimize treatment [41]. In a donor-lung with NPE, pre-transplant use of ex vivo lung perfusion can increase the percentage of used donors by acting on modifiable selection criteria such as oxygenation, contusion, and pulmonary infiltrates [50].

Prognosis

Since the mortality rate of NPE is between 60 and 100% [1], the prognosis is generally poor [1]. Introduction of ECMO in the acute management of NPE patients, however, may improve the outcome of NPE patients. Despite the application of ECMO, however, fatalities may still occur, most frequently due to the severity of the cerebral lesion [46]. Since mortality of NPE is higher than that of TTS, NPE is more likely to be responsible for SUDEP than TTS.

Discussion

This review shows that the types of cerebral disease triggering NPEs are more widespread than so far anticipated. Nonetheless, the most frequent triggers are brain-

stem encephalitis in hand-mouth-foot disease, SAB, ICB, TBI, and epilepsy. Brain surgery, subdural hematoma, EDH, ischemic stroke, cerebral mass lesions, electroconvulsive therapy, intoxications, or hydrocephalus are more rare triggers of NPE. An interesting finding in a small portion of patients is the co-occurrence of TTS with NPE. The rare co-occurrence of TTS and NPE suggests a common pathomechanism. An argument for the same pathomechanism responsible for TTS and NPE is that type and frequency of neurological triggers are similar. Another similarity is that massive endogenous stress is required for triggering the event. Another strong argument for a causative relation between NPE and TTS is Inamasu's study in which 14 patients with SAB simultaneously developed NPE and TTS [34]. The pathophysiologic background of NPE is distinct from that of pulmonary edema due to cardiac or other pulmonary disease. Despite the recent progress in the elucidation of pathophysiological aspects of NPE, treatment remains supportive and should target the neurological disease and the pulmonary disorder. Recognition of NPE in time is crucial due to its impact on treatment, prognosis, and

management of donor lungs. In conclusion, CNS-disease triggering NPE is more variegated than anticipated. Delineation of NPE from other pulmonary or cardiac conditions mimicking NPE is crucial to initiate appropriate measures and improve the outcome of these patients.

Disclosure Statement

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Author Contribution

J.F. was responsible for the design, literature search, discussion, first draft, and for providing critical comments.

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