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CASE REPORT **INTNSIVE CARE**

Neurogenic pulmonary edema: a case report and literature review

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ABSTRACT

We report a case of neurogenic pulmonary edema (NPE) caused by an intraparenchymal bleed following a fall. We review the literature regarding the pathophysiology, clinical presentation, and management of neurogenic pulmonary edema.

Pulmonary edema is the accumulation of fluid within the alveolar and interstitial spaces; one of the lesser-appreciated causes is neurogenic. NPE occurs following acute central nervous system (CNS) injury and is often rapidly developing in nature. Common insults include epileptic seizures, traumatic brain injury, intracranial hemorrhage, and pediatric encephalitis

The low prevalence of NPE and the distracting primary disease often divert physicians' attention away from its prompt diagnosis, this is regrettable as up to 35% of patients with intracranial hemorrhage have NPE.

NPE is a prevalent yet underdiagnosed disease. The underlying mechanisms are still debatable and much more research is required to diagnose and treat the condition effectively. Treatment is mainly supportive with judicious use of invasive ventilation and management of primary pathology. We aimed to refresh the knowledge of young clinicians regarding NPE.

Abbreviations: AVM - arteriovenous malformation; CNE - central nervous system; NPE - Neurogenic pulmonary edema; SAH - subarachnoid hemorrhage; SUDIP - sudden unexplained death in epilepsy

Keywords: Neurogenic, Pulmonary edema, Pathophysiology, Presentation, Prevalence, Treatment.

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1. INTRODUCTION

Neurogenic pulmonary edema (NPE) is an acute accumulation of fluid within the alveoli that occurs following a range of varied neurogenic insults such as epileptic seizures, traumatic brain injuries, intracranial hemorrhages, pediatric encephalitis, cerebral or spinal surgery, Moya-Moya disease, vasculitis, amyloid angiopathy, and mass lesions.[1,2] While head trauma continues to be the most prevalent cause, 80% of non-traumatic cases are caused by ruptured intracranial aneurysms.[2]

NPE can clinically present with an array of symptoms such as dyspnea, tachypnea, and tachycardia with

possible frothy sputum.[3] Chest auscultation is significant for bilateral crackles, which on x-ray presents as bilateral alveolar opacities.[1] Clinical manifestations usually resolve within 48 h in 50% of the patients.[1,2] Exclusion of cardiogenic pulmonary edema is achieved through echocardiography and clinical context.[4-6] The fact that several more prevalent conditions mimic NPE and that there is no reliable tool to diagnose NPE means that a high index of suspicion, clinical context, and exclusion of other diagnoses is necessary to reliably diagnose NPE.[2]

While diagnosing NPE proves to be a serious challenge, it is nevertheless of paramount importance for urgent management of the condition. A meta-analysis looking at the prevalence and in-hospital mortality of NPE following subarachnoid hemorrhage (SAH) found that the pooled global prevalence of NPE was estimated to be 13% with an in-hospital death rate of 47%. The occurrence of NPE was found to have a bimodal distribution with the highest prevalence occurring within hours following initial SAH and 12-24 h afterwards.[2] Another study investigating NPE in patients with SAH found its prevalence to be 4.6%.[7] An article exploring the causes of sudden unexplained death in epilepsy (SUDEP) found that 233 (71%) cases of 326 had pulmonary congestion and edema.[3]

Although neither specific nor sensitive diagnostic tests are currently available, independent predictors for NPE (such as in patients with subarachnoid hemorrhage) can help physicians keep NPE as a differential. Predictors such as World Federation of Neurological Surgeons (WFNS) grading class of SAH, female gender, APACHE II score ≥ 20, IL-6 > 40 pg/mL, Hunt and Hess grade ≥ 3, elevated troponin I, elevated white blood cell count, and electrocardiographic abnormalities have shown correlations with NPE.[2]

2. CASE REPORT

An 11-year-old, previously healthy female child, presented to a health facility following a standing fall. Immediately afterward, she reported severe headache, numbness, and pain over her left thigh and arm along with profuse nasal bleeding. The patient had documented generalized tonic-clonic fits. A Glasgow Coma Scale (GCS) of 8/15. She had a single episode of vomiting. She was subsequently transferred to the Shifa International Hospital Emergency Room (ER), a tertiary care center, where she was found to have bradycardia, hypotension, a GCS of 5/15, and bilateral coarse crackles with progressively rising oxygen dependency. Her oxygen saturation was 70% on 10L/min of oxygen. The child was immediately intubated and pink frothy fluid about 400 ml was suctioned. Initial ventilator settings included a tidal volume (Vt) of 400 ml, inspired oxygen fraction

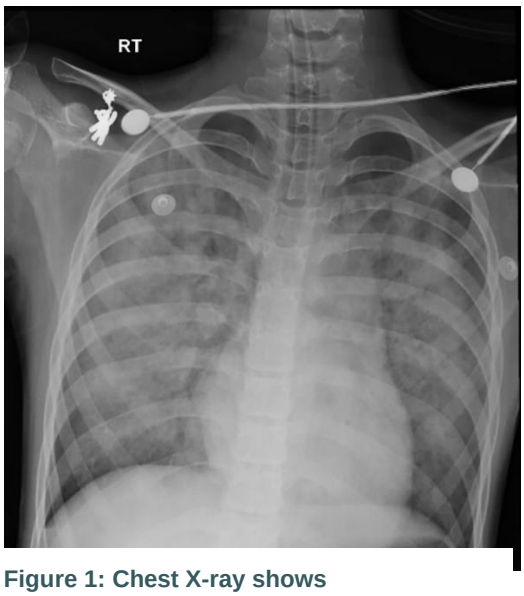

Figure 1: Chest X-ray shows Inhomogeneous opacifications in both lungs

(FiO_2) of 100%, respiratory rate 20/min, positive end-expiratory pressure (PEEP) 10 cmH_2O, and a peak inspiratory pressure (PIP) 30 cmH_2O.

Chest X-ray (Figure 1) was performed and revealed inhomogeneous opacifications in the lungs bilaterally. CT scan of the head was significant for right-sided frontoparietal hemorrhage with contralateral midline shift, right-sided uncal herniation, and cerebral arteriovenous malformation (AVM) (Figure 2).

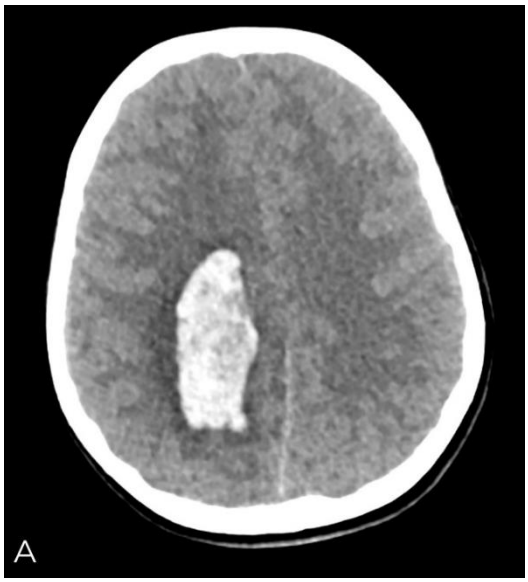

Figure 2: CT brain without contrast. Intraparenchymal hemorrhage in the right frontoparietal region seen.

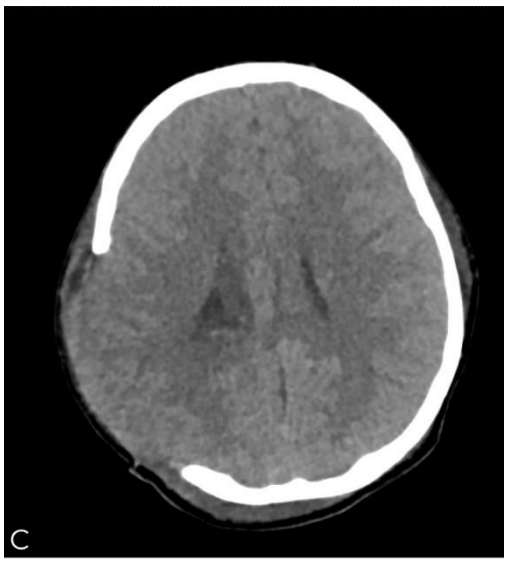

Figure 3: CT without contrast of the brain, after right parietal decompressive craniectomy and evacuation of the hematoma.

Emergent neurosurgical intervention was undertaken with a right-sided decompressive craniectomy with evacuation of the clot and excision of the AVM

performed (Figure 3).

The patient was then shifted to the ICU, where she was afebrile, tachypneic, and tachycardic. Chest auscultation was significant for bilateral crackles, coupled with escalating ventilatory requirements. An electrocardiogram (ECG) and echocardiography ruled out cardiogenic dysfunction and AVM of the chest was also ruled out by CT because of persistent excessive tracheal secretions post-surgical intervention. Lab workup was done and the sepsis profile was found to be negative (Table 1). Having excluded the more common causes, a diagnosis of NPE due to SAH was made. The

Table 1: Laboratory work-up

Test	Result	Reference range
pH	7.26	7.35-7.45
PCO2	45.1 mm Hg	32-48
PO2	46.9 mm Hg	83-108
HCO3	19.9 mmol/L	22-29
Base Excess	-6.9 mmol/L	-2-+2
SpO_2	74.4 %	94-98
LDH	522 U/L	135-214
Antinuclear Antibody	Negative	
Von Willebrand Factor	220.7	60-142

patient was kept intubated and sedated and her hemodynamics were optimized. Infusion of loop diuretics was started for edema. Over the next few days, the patient had a gradual improvement in her symptoms allowing her ventilation to be tapered off. On the 6th day of intubation, she was gradually weaned of the ventilator. She was then successfully extubated to a low-flow nasal cannula at 3 L of oxygen and continued to remain vitally stable thereafter. Her repeat chest X-ray showed a resolution of infiltrates, and she was shifted to the floor and then finally discharged home.

3. DISCUSSION

Although NPE has been widely reported, its pathophysiology remains a topic of hot debate. Current understanding places it as an interplay between sympathetic nervous system activation and altered pulmonary capillary pressure and permeability. Lesions in the medulla oblongata through catecholamine excess lead to NPE.[3,8] The role of sympathetic excess serving as the basis of NPE is emphasized by the concomitant presence of Takotsubo cardiomyopathy in many patients with NPE, a disease that has been known to stem from catecholamine excess.[3]

Sympathetic stimulation leads to increased vasoconstriction in both pulmonary and systemic circulations. It is also responsible for increased cardiac output, which leads to increased systemic pressures forcing blood into the lower-pressure pulmonary circulation.[9] The increased pulmonary pressures damage the alveolar-capillary membrane which causes an increase in the pulmonary capillary pressures and permeability leading to increased fluid accumulation and edema formation.[1,2]

Neurogenic injury directly leads to the release of inflammatory markers that increase pulmonary permeability. Neuropeptide Y (released in response to norepinephrine), alpha-adrenergic agonists, and pro-inflammatory mediators (released in response to brain injury) have all been implicated in causing NPE. B1-adrenoceptors have also been implicated in over-perfusion and edema of the lungs due to increased right ventricular systolic pressure.[2]

Cardiac dysfunction is visualized on ECG with abnormal Q or QS waves, nonspecific ST or T wave change, and with increased cardiac biomarkers, such as troponin. These findings have been seen as predictors of NPE. This is mainly from the connection of norepinephrine being released from the cardiac nerves causing coronary vasospasm. Lactate build up occurs as a result of cardiac dysfunction leading to lactate serving as an independent factor associated with early onset of NPE.[2] Given the sympathetic nature of NPE's pathology, adequate

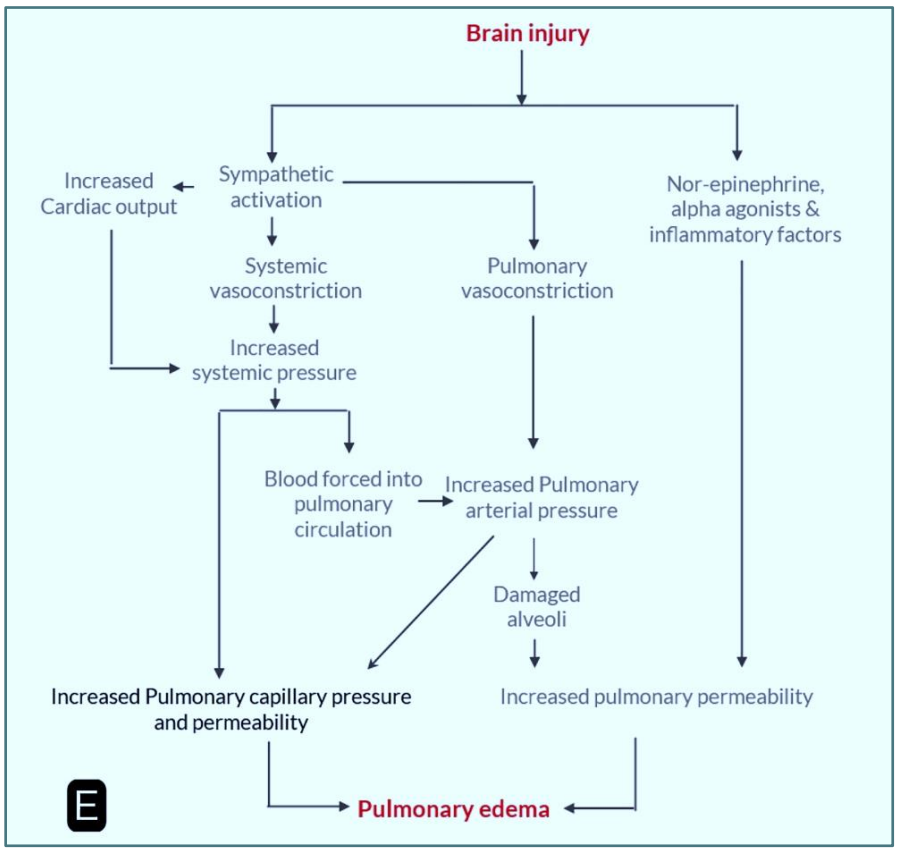

Figure 3: Pathophysiology of neurogenic pulmonary edema

sedation, analgesia, and sympathetic suppression have been hypothesized to reduce its incidence.[1]

The treatment of NPE remains a focus of continuous research, focusing both on management of NPE as well as the primary insult.[3] Prompt treatment of aneurysms through craniotomy and clipping or endovascular intervention with coils and stents is needed to prevent rebleeding.[9] Intubation plays a critical role in managing patients and a fine balancing act is necessary to maximize the patient's recovery. The cornerstone of this is adequate positive end-expiratory pressure (PEEP). While on one hand increasing PEEP leads to increased alveolar recruitment, which improves oxygenation, it also leads to increased intrathoracic pressure which could theoretically reduce cerebral venous outflow worsening the intracranial pressure. Keeping ICP in mind a PEEP < 15 cmH_2O has been recommended.[3]

Hemodynamics of the patient must be optimized to reduce systemic pressure while at the same time improving cardiac output. Dobutamine through its highly selective β-1 activation increases cardiac inotropy and dilates blood vessels and has been used to treat patients with NPE. Another drug with potential is levosimendan, which not only promotes vasodilatation and exerts organ-protective effects through the activation of the adenosine triphosphate-sensitive potassium (KATP) channels, but also enhances myocardial contractility via calcium sensitization of cardiac troponin C in combination with the effects of anti-oxidation, anti-myocardial apoptosis, and anti-myocardial stunning.[3]

Extracorporeal membrane oxygenation is another strategy that can be used in more severely afflicted patients, but its use is limited by the need for anticoagulation which at times goes directly against the primary brain injury.[3]

The early initiation of treatment is also helpful in reducing the hospital stay of these patients, which helps reduce the many complications these patients may face., including sepsis, urinary tract infections, aspiration pneumonia, nutritional deficits, deep venous thrombosis, and anemia.[2]

4. CONCLUSION

The relationship of the neurological injury with pulmonary edema and its pathophysiology remains poorly understood. The most probable cause is that the neurological injury leads to subsequent sympathetic activation and altered pulmonary capillary pressure as well as permeability. Treatment remains largely supportive with reversal of neurological injury.

5. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

6. Ethical considerations

The written consent was obtained from the parents of the patient to publish this case report as an academic service.

7. Authors' contribution

DS, MM, MS: Data collection, literature review

SF: Concept

AK: Proofreading

HA: Editing the proof

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