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Review Article

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Neurogenic pulmonary oedema

Habib U Rehman
Department of Medicine, Hull Royal Infirmary, Hull, United Kingdom

Abstract

Although neurogenic pulmonary oedema is an uncommon condition, it is found in 20% of victims with severe head injury. The onset is typically rapid with development of dyspnoea, cyanosis and hypoxia suddenly and unexpectedly after an intracranial injury. The pathogenesis is not entirely clear, but both increased hydrostatic pressure and capillary permeability are incriminated. It is important to differentiate neurogenic pulmonary oedema from aspiration pneumonia, because the treatment of the two conditions differ. A combination of measures to reduce intracranial pressure, optimize body oxygenation, decrease pre- and after-load and improve cardiac contractility is the mainstay of treatment. Mortality is high despite these measures.

Key words: *head injury, neurogenic, pulmonary oedema.*

Introduction

Acute neurogenic pulmonary oedema has been reported with several neurological disorders including severe head injury,[1] subarachnoid haemorrhage,[2] cerebral thrombosis,[3] intracerebral haemorrhage,[4] intracranial tumours,[5] induction of anaesthesia[6] and generalized tonic clonic convulsions.[7] Fulminant neurogenic pulmonary oedema has been described in a patient with hand, foot and mouth disease due to direct invasion of spinal cord and medulla by enterovirus 71.[8] Shanahan first described acute neurogenic pulmonary oedema in 1908.[9]

The true incidence of neurogenic pulmonary oedema is not known, but pathological data indicate that it is common in people who die of head injuries[10] and in those who die during or shortly after an epileptic fit. An autopsy series of Vietnam combat casualties who died of isolated head injuries reported that 85% experienced pulmonary oedema.[11] Bratton and Davis reported neurogenic pulmonary oedema in 20% of patients with severe head injury (Glasgow Coma Scale score of 8 or less) (Fig. 1).[12]

Clinical features

The onset of neurogenic pulmonary oedema is typically rapid. The patient is usually a child or a young adult with a history of recent intracranial injury. It may develop within minutes of blunt head injury.[13] Although classic neurogenic pulmonary oedema has an immediate onset and becomes clinically recognizable 2–12 h after injury, clinical onset may be delayed for 12 h to several days. Dyspnoea, cyanosis and hypoxia develop suddenly and unexpectedly. The patient may be peripherally shut down, with a rapid weak pulse, pallor and sweating.

The important differential diagnosis is from aspiration pneumonitis, which is common in these patients. The radiographic features of aspiration pneumonitis usually evolve over a period of hours and may take 3 weeks to resolve, whereas the alveolar

Correspondence: Dr HU Rehman, Hull Royal Infirmary, Hull HU3 2JZ, United Kingdom. Email: habib@rehman786.freeserve.co.uk

Habib U Rehman, MRCP, Specialist Registrar, Department of Medicine.

infiltrates of neurogenic pulmonary oedema occur immediately after the injury.[14] (Fig. 2)

Pathophysiology

Pathophysiology of neurogenic pulmonary oedema is poorly understood, but probably both hydrostatic pressure and altered capillary permeability play a part in the pathogenesis, in addition to depressed myocardial function. An initial hyperdynamic cardiovascular response to severe head trauma leads to elevations in blood pressure, heart rate and cardiac output.[15] This response appears to be sympathetically mediated. Hypothalamus, nucleus tractus solitarius and area postrema of the medulla have been implicated in this hyperdynamic response.[16] This response may be blocked by β-receptor antagonists[17] and inhibition of catecholamine release.[17]

A direct neurogenic cause of neurogenic pulmonary oedema is suggested by the following observations: (i) increased pulmonary vascular permeability and development of acute pulmonary oedema following raised intracranial pressure in experimental animals;[18,19] and (ii) the protective effect of prior pulmonary denervation,[20] transected cervical cord[11] or pretreatment with α-adrenergic blocking agents.[21]

Increased intracranial pressure causes α-adrenergic stimulation, resulting in generalized vasoconstriction and elevated systemic and pulmonary arterial and venous pressures.[22] This sympathetic response may be due to disturbance of hypothalamic function, since experimental hypothalamic lesions have been shown to cause pulmonary oedema.[23] However, Bratton and Davis[24] did not find any correlation between specific anatomical lesions diagnosed by cranial computed tomography (CT) scans and neurogenic pulmonary oedema. This may be due to the limited resolution of CT for the brain-stem.

The effect of this sympathetic response is a massive transfer of blood from the systemic to the pulmonary circulation, resulting in hydrostatic oedema. Pulmonary oedema persists and increases in volume, despite the return of pressures to normal. This may be due to hydrostatic damage to the pulmonary endothelium, causing a permeability defect and resulting in a high protein content of the interstitial fluid.[25,26]

Pulmonary capillaries have extremely thin walls and raising the capillary pressure results in greatly increased stresses on the capillary walls. Ultrastructure damage to the walls is seen at pressures of 40 mmHg and above.[27] These changes include breaks in the capillary endothelial layer, alveolar epithelial layer and sometimes all layers of the wall. The very high catecholamine concentrations in the blood in neurogenic pulmonary oedema are associated with high pulmonary arterial and wedge pressures.[28]

Severe depression of myocardial function has also been reported in neurogenic pulmonary oedema, as evidenced by markedly depressed cardiac index and left ventricular stroke work index, and substantially elevated pulmonary artery wedge pressure, systemic vascular resistance index and pulmonary vascular resistance index.[29]

Acute inhibition of nitric oxide synthase in brain-injured rats has been shown to increase mortality, possibly because of its cardiovascular effects.[30] Nitric oxide synthase is formed from the substrate L-arginine. Impaired nitric oxide function results in an impairment of endothelium-dependent vasodilatation. Nitric oxide has a number of other important functions in the vessel wall, such as inhibition of platelet aggregation and of adhesion molecule expression, prevention of smooth muscle proliferation and modulation of vascular growth.[31]

- Head injury
- Subarachnoid haemorrhage
- Cerebral thrombosis
- Intracerebral haemorrhage
- Intracranial tumours
- Tonic clonic convulsions

Figure 1. Causes of neurogenic pulmonary oedema.

- Rapid onset
- Unexpected development of dyspnoea
- Cyanosis and hypoxia
- Rapid weak pulse
- Pallor
- Sweating

Figure 2. Clinical features of neurogenic pulmonary oedema.

A role for endothelin in the pathogenesis of neurogenic pulmonary oedema has also been suggested by experiments on rats, where there was a time-dependent increase in endothelin-1 levels in bronchoalveolar lavage associated with a raised mean arterial blood pressure and end-inspiratory airway pressure and a drop in arterial oxygen partial pressure with rapid development of pulmonary oedema. Pre-treatment with endothelin-converting enzyme inhibitor afforded protection from hypoxia and significantly reduced peak endothelin-1 levels in bronchoalveolar lavage fluid.[32]

The importance of the role of endothelin is also supported by another experiment where intrathecal injection of endothelin-1 and endothelin-3 enhanced vascular permeability in the lungs by 22-fold and seven-fold, respectively. This was in contrast to intravenous injection of endothelin, which failed to produce lung oedema. Prior intrathecal injection of a selective endothelin receptor antagonist prevented the increases of lung vascular permeability and oedema. Intravenous treatment with phentolamine or pentolinium also abolished the lung vascular permeability changes evoked by endothelin-1. Furthermore, the effects of endothelin-1 were almost abolished in rats subjected to sympathectomy.[33]

These results suggest that the increases of pulmonary vascular permeability are due to an intense vasoconstriction mediated by α-adrenoceptors following the release of catecholamines in response to intrathecal injection of endothelin-1, which activates the endothelin-A receptors in the spinal cord. Endothelin is the most potent mammalian vasoconstrictor yet discovered.[34] Its three isoforms play important roles in regulating vascular tone. The isoforms bind to two major receptor subtypes (ETA and ETB) which mediate a wide variety of physiological actions in several organ systems. Specific and non-specific receptor antagonists and endothelin-receptor enzyme inhibitors have been developed which interfere with endothelin's function. In animals, an orally active ETA and ETB receptor-blocking agent, bosentan, has been shown to prevent hypoxia-induced pulmonary hypertension and pulmonary artery remodelling.[35]

Treatment

A logical approach to the treatment of neurogenic pulmonary oedema involves a combination of measures to reduce intracranial pressure and block the peripheral effects of sympathetic activity. Attempts should be made to optimize body oxygenation, decrease pre- and after-load and increase myocardial contractility.

Thiopentone sodium depresses the central nervous system activity and metabolism, thereby reducing the cerebral blood flow and hence intracranial pressure.[36] There is conflicting evidence about the potential effect of positive end expiratory pressure on intracranial pressure. Controlled intermittent positive pressure ventilation causes local reflex cerebral vasoconstriction in response to the reduction of $P\text{aCO}_2$. This results in a fall in intracranial pressure. Care must be taken to avoid reducing the $P\text{aCO}_2$ below 30 mmHg because this may result in cerebral hypoxia. Surgical decompression may result in dramatic clinical improvement.[36]

Alpha-receptor-blocking agents, such as phentolamine and phenoxybenzamine, have been used with success. Droperidol has theoretical advantage as it has alpha-receptor-blocking properties and it reduces cerebral metabolism.[37] Since neurogenic pulmonary oedema is generally associated with severe depression of myocardial function, dobutamine has been successfully used to reverse this dysfunction.[29]

Diuretics and fluid restriction are useful, but extreme care must be taken, as a proportion of these patients may be hypovolaemic.

Conclusion

Acute neurogenic pulmonary oedema is an uncommon condition, occurring in association with a wide variety of neurological insults. Mortality is high and may exceed 90%.[38] An awareness of the condition and its treatment is important, since it may improve the degree of recovery. In the future, treatment with nitric oxide analogues and endothelin-receptor antagonists holds promise.

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