**Increased Intracranial Pressure and Pulmonary Edema**

**Part 1: Clinical Study of 11 Patients**

THOMAS B. DUCKER, CAPTAIN, MC, USAR

*Division of Surgery, Walter Reed Army Institute of Research, Washington, D.C., and the Neurosurgery Section, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan*

PULMONARY abnormalities such as pulmonary edema, bacterial and viral pneumonia, and aspiration pneumonitis have frequently been reported in association with intracranial disease. Pulmonary edema often arises as a pathophysiological hemodynamic response to the intracranial disease without the complication of other etiologic agents. This report is an analysis of 11 such cases. All were young patients without primary cardiopulmonary disease.

**Case Reports**

*Case 1.* A 12-year-old boy was struck on the head by an hockey stick. He was not immediately knocked unconscious, but 30 minutes after the accident he was semicomatose, had a dilated right pupil, and bilateral Babinski signs. He moved all four extremities in response to painful stimuli. Blood pressure was 124/78, pulse was 48.

*Surgical treatment.* During the next 20 minutes, he was intubated and prepared for surgical decompression. Suddenly, a pink frothy foam began to pour out of the endotracheal tube. Burr holes were hastily made, and an epidural hematoma removed from the left parieto-occipital region. Both pupils then became small, and the boy moved all four extremities. Blood pressure was 100 systolic, pulse 124. He had received less than 100 cc of intravenous fluid. Central venous pressure was 4 cm H$_2$O. Cardiac stimulants, rapid digitalization, and tracheal suction failed to alter the severe pulmonary edema. He became progressively hypoxic and died 4 1/2 hours after injury.

*Autopsy findings.* At autopsy it was found that the epidural hematoma had been removed and there was no discrete lesion of the central nervous system, only moderate, generalized cerebral edema. The lungs showed a noncellular foamy edema and weighed 780 gm on the right and 750 gm on the left, compared to a normal weight of 250 gm per lung for his size.

*Case 2.* A 12-year-old girl collapsed suddenly while getting dressed. On the way to the hospital, she thrashed about and had clonic seizure movements; within 30 minutes, she was semicomatose.

*Examination.* There was a hemorrhage in the optic disc, right-sided hyperreflexia, and a Babinski sign on the right. A lumbar puncture demonstrated bloody fluid under pressure of over 500 mm H$_2$O. Soon thereafter, she developed bilateral, evenly distributed rales and was foaming at the mouth. Respirations ceased. Endotracheal positive pressure ventilation and cardiac stimulants helped clear the pulmonary edema, but she never again had spontaneous respiration. Slowly, all spontaneous movements stopped, and both pupils became dilated without reaction to light. Death occurred the next day.

*Autopsy findings.* Autopsy revealed a massive intraventricular hemorrhage, the origin of which was not apparent. The right lung weighed 350 gm and the left 550 gm, compared to a normal weight of 250 gm per lung for her size.

*Case 3.* A 17-year-old girl developed headaches and progressive mental dullness. The neurological examination was normal, but skull x-rays showed evidence of increased intracranial pressure and an enlarged sella turcica. Electroencephalogram and brain scan were normal. Endocrine studies indicated minimal panhypopituitarism. An air ventriculogram revealed stenosis of the aqueduct of Sylvius.

*Surgical treatment.* Six hours after the air study, the patient became very stuporous, without localizing neurological signs. In the next few minutes, she developed respiratory distress, pharyngeal congestion, and diffuse rales. The intracranial cerebrospinal fluid pressure (over 250 mm H$_2$O) was reduced by

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needle ventriculostomy. Endotracheal suctioning and positive-pressure breathing, digitalization, and steroids (after the reduction of intracranial pressure) helped to improve her condition; the central venous pressure was 4 cm H₂O when the intravenous isoproterenol drip was started. With ventriculostomy drainage and intermittent positive-pressure breathing over the next week, the pulmonary congestion cleared. Thereafter, she had a ventriculostomy shunt.

Postoperative course. The course was complicated by a postoperative subdural hematoma; after hematoma removal and a shunt revision, the patient improved steadily and was discharged doing well. She continues to be well 1 year later.

Case 4. A 19-year-old boy suffered a severe closed head injury and a linear basilar skull fracture in an auto accident.

Examination. The patient was still unconscious 1 hour later, responding only to painful stimuli. Both pupils were small, and he had bilateral Babinski signs. The pulse was 64 and blood pressure 160/50. In the next hour he developed decerebrated posturing to painful stimuli. Suddenly, he had bilateral rales and rhonchi. An intravenous drip was started immediately, and the central venous pressure was 6 cm of water.

Tracheostomy, positive-pressure respiration, antibiotics, and steroids were all started. The patient improved initially but required vigorous tracheal suction of a pink foamy material. Over the next 24 hours, he was hyperthermic and remained decerebrate; the pupils dilated slowly and became fixed to light. He died 36 hours after the injury.

Autopsy findings. There was generalized encephalopathy, cerebral edema, and uncal herniation. The right lung weighed 1025 gm and the left 950 gm, compared to a normal weight of 350 gm per lung for his size.

Case 5. A 19-year-old boy was shot in the right occipital region. The injury immediately rendered him semicomatose with a left hemiparesis.

Surgical treatment. The emergency treatment included debridement and primary closure with a dural graft. He improved steadily and 3 weeks later was talking and had only minimal weakness on the left side. Soon thereafter he was found semicomatose with a left hemiplegia. The pulse was 76 and blood pressure 120/76. One hour later, he became cyanotic, had diffuse pulmonary rales, and began to foam at the mouth. A tracheostomy was performed and positive-pressure respirations started. The central venous pressure was 5 cm H₂O. A large subdural hematoma beneath the dural graft was removed 1 hour later. However, the patient continued to deteriorate and died within 4 hours of his being found unconscious.

Autopsy findings. Autopsy showed that the hematoma had been removed; there was evidence of uncal herniation. The right lung weighed 910 gm and the left 840 gm; there was histological evidence of pulmonary edema.

Case 6. A 22-year-old nurse had increasingly severe headaches for 4 months followed by staggering and a tendency to fall to the right. Examination showed early papilledema, dysmetria, and dysdiadochokinesia on the right, and falling to the right on Romberg testing. Skull films were normal, but a brain scan suggested a right-sided posterior fossa tumor. An air ventriculogram disclosed a dilated ventricular system except for the fourth ventricle, which was displaced to the left.

Surgical treatment. A posterior fossa craniotomy was performed with total excision of a cerebellar astrocytoma. In the postoperative period, she had depressed respirations initially, but by the next day her condition had improved.

Twenty-four hours after operation, her respiration became rapid and shallow and her lungs contained audible rales. Digitalis and aminophylline were started, and the edema subsided somewhat. The electrocardiogram was normal; the central venous pressure was 6 cm water. Her level of consciousness deteriorated. Steroids and mannitol were used to combat cerebral edema. Ventricular tap and arteriograms failed to reveal hematoma formation. The patient's condition slowly became worse and she died 48 hours postoperatively, 24 hours after developing pulmonary edema.

Autopsy findings. Autopsy showed that the tumor had been removed but that there was unexplained extensive cerebral edema. The lungs were found to be diffusely edematous, weighing 910 gm on the right and 840 gm on the left.

**Examination.** Six hours later he was admitted unconscious with a right hemiparesis and left fixed dilated pupil. Within minutes of admission, he started foaming at the mouth and had bilateral pulmonary rales. Blood pressure was 170/100, pulse 64, and central venous pressure 2 cm of water. Concentrated glucose (100 gm) was given intravenously. The patient died 30 minutes after admission.

**Autopsy findings.** There was a large left epidural hematoma. The lungs were edematous, weighing 940 gm on the right and 880 gm on the left.

Case 8. A 31-year-old woman became suddenly unconscious at work.

**Examination.** Thirty minutes later, the blood pressure was 110/60, pulse 100, and respirations 30. The pupils were miotic, the head and eyes were deviated to the right, and there was a left hemiparesis. She was hypo-reflexic with equivocal pathological reflexes. Heart and lung examinations were normal. Skull x-rays were normal. A lumbar puncture revealed bloody fluid under pressure of over 300 mm of water.

One hour after collapsing, she developed a respiratory rate of 50 and had diffuse bilateral coarse rales. Blood pressure remained in the range of 110-130/75-90, pulse 100-112. There was foam in her pharynx, and respirations increased to 64. Central venous pressure was 0 to 2 cm of water. Supportive measures were initiated but the patient died.

**Autopsy findings.** Autopsy showed the source of the subarachnoid hemorrhage to be a 10 mm aneurysm on the left internal carotid artery. The lungs were diffusely hyperemic weighing 840 gm on the right and 910 gm on the left. Cut section showed that pink frothy fluid flowed freely from the alveolar spaces and bronchi.

Case 9. A 32-year-old man was in an auto accident and was rendered unconscious immediately.

**Examination.** One hour later, he was comatose with pinpoint pupils; he showed decerebrate posturing in response to painful stimuli. The blood pressure was 140/84, pulse 88, and respiration 32. X-rays showed no fractures. Within 30 minutes after admission, respirations rose suddenly into the 60's and the patient had pulmonary rales and pharyngeal foam. Endotracheal-assisted positive-pressure breathing and dexamethasone in high doses were started. Over the following hour, he improved. A nasogastric tube was placed because of hematemesis. Central venous pressure was 2 cm of water. Blood pressure was now 110/62 and pulse 120. Over the next 24 hours, the central venous pressure was always below 5 cm water, but the patient required six units of blood to maintain a systolic pressure over 110 and a pulse below 110. Respiratory assistance with positive pressure was maintained during this period. The patient was slowly digitalized. However, he died 24 hours after injury.

**Autopsy findings.** The brain was very confused, with diffuse early softening. The stomach showed diffuse petechial hemorrhages. The lungs were very congested with hemorrhages, edema, and weighed 1405 gm on the right and 1220 gm on the left.

Case 10. A 43-year-old man was in an auto accident and rendered unconscious for a few minutes. He recovered uneventfully and had no neurological deficit. Some 14 days later, headaches appeared.

**Examination.** The patient was admitted 22 days after the accident in a stupor. His pupils were enlarged but reactive; there was right hemiparesis and right hyperreflexia with a Babinski sign.

**Surgical treatment.** A left subdural hematoma was drained through burr holes on that day. The following day function returned on the right side but 3 days postoperatively he became very restless and required paraldehyde for sedation. The blood pressure was 128/84, pulse 84, and respirations 80. He had a right-sided clonic tonic seizure, which progressed to a grand mal convolution. Approximately 30 minutes later, his respiration was 60-70 per minute while other vital signs remained stable. Increased pharyngeal secretions and bilateral pulmonary rales were then noted for the first time. His blood pressure dropped to 70 systolic. Central venous pressure was only 4 cm water. The hematocrit was 45%; 2000 cc of Ringer’s lactate were given intravenously to maintain blood pressure.
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However, the urinary output dropped, and the level of consciousness deteriorated. The patient died 12 hours after the seizure.

**Autopsy findings.** There was a mild cerebral edema and a 1-cm rim of subdural hematoma on the left. No specific cerebral lesion could be found to account for the seizure. The lungs were the only congested organ, weighing 790 gm on the right and 770 gm on the left.

**Case 11.** A 44-year-old man developed severe headaches one afternoon, and collapsed suddenly the following morning.

**Examination.** On admission approximately 40 minutes later, the patient was in a deep coma, had Cheyne-Stokes’ respirations, pharyngeal foam, and bilateral pulmonary rales. He was immediately intubated, and positive pressure respiration was instituted. The blood pressure was 96/70 and pulse 104. He was rapidly digitalized. Aminophylline and sodium bicarbonate were given. The right pupil became dilated and fixed to light. The blood pressure dropped to 70/50, and the heart rate rose to 160. Respiratory assistance became necessary. Both pupils became dilated, and bilateral retinal hemorrhages were seen. Lumbar puncture revealed bloody fluid under pressure greater than 500 mm water. The patient became cyanotic and died 2½ hours after his collapse.

**Autopsy findings.** There was subarachnoid hemorrhage secondary to a ruptured anterior communicating artery aneurysm. The lungs were congested, weighing 900 gm on the left and 1000 gm on the right.

**Discussion**

A variety of central nervous system conditions, including CNS trauma, hemisphere, neoplasm, and seizure disorders, have been found to be associated with an equally wide variety of pulmonary lesions. It is well understood that central nervous system disease may predispose bacterial, aspiration, or hypostatic pneumonias. In our series, there were no patients with evidence of aspiration. All patients with cellular inflammation or with lung or tracheal cultures positive for bacterial pathogens were rigorously excluded. In this way, it has been possible to accumulate a significant series for the analysis of pulmonary edema associated with central nervous system disease. This association has frequently been noted in the Japanese and British literature, but only occasionally by American neurologists.

The autopsy incidence of the association of pulmonary edema with central nervous system disease ranges from 11% to 28%. Most instances of pulmonary edema of this type have been associated with primary cardiopulmonary disease. It is also found in renal, hepatic, and hematological diseases. In our 11 cases, however, the pulmonary edema occurred in relatively young patients, none older than 45, without any evidence of primary disease in the heart, lungs, liver, or kidneys. When initially examined upon admission, all patients were found to be normal except for the central nervous system findings. We excluded patients in whom pulmonary problems developed secondary to thoracic trauma.

Each of the patients reported in this series developed massive pulmonary edema while under hospital observation; no patient had received more than 500 cc of parenteral fluid at the time the pulmonary complication developed. Nine of the 11 patients had normal central venous pressure by actual measurement. No cardiac arrhythmias were noted. None of the patients responded to digitalis or to positive-pressure respiration with the expected resolution of edema. At autopsy, the only abnormalities were in the central nervous system. The lungs were uniformly heavy, hyperemic with foam in every bronchial and alveolar space on cut section. Histological examination showed a uniform noncellular edema throughout both lungs.

A number of central nervous system lesions were present, the only common feature being a rather sudden increase in intracranial pressure in 10 of 11 patients. Cerebrospinal fluid pressures were uniformly elevated when measured. Uncal herniation and cerebral edema were common autopsy findings. In the single survivor, prompt clinical improvement followed ventriculostomy. The sole instance where intracranial pressure was probably normal was in Case 10; this patient developed pulmonary edema following a seizure in the postoperative period after evacuation of a subdural hematoma.

The pathophysiological circumstances by which increased intracranial pressure or massive central nervous system discharge predis-
poses the sudden development of pulmonary edema is unknown. We have been able to reproduce pulmonary edema in dogs by increasing intracranial pressure either by inflation of a subdural balloon or by the introduction of bloody saline into the cisterna magna. Similar studies have been carried out by Campbell. In fact, neurogenic pulmonary edema can be produced by a variety of conditions. In the experimental animal these include specific neuronal alterations, such as stimulation of the hypothalamic nuclei, or destruction of the preoptic nuclei bilaterally, or nonspecific stimuli such as intracisternal injection of fibrin or endotoxin. On the other hand, lesions of the ventromedial hypothalamus can protect against pulmonary edema induced by preoptic nuclear destruction. Efferent hypothalamic pathways descend through the brain stem and carry autonomic stimuli into the lateral and ventral funiculi of the spinal cord. Just before reaching the reticular formation in the medulla, fibers are given off to the respiratory and vasomotor centers. These medullary centers are sensitive to raised intracranial pressure and theoretically could be stimulated indirectly or directly.

It is equally possible that more peripheral autonomic pathways are involved. Capillary permeability, sympathetic tone, and parasympathetic impulses have each been considered. Even total denervation of the lung has been carried out to support the thesis that the systemic vascular bed controls pulmonary vascular pressure. It is hoped that future studies will more clearly define the pathophysiological mechanisms involved.

It is apparent from our 11 cases that the usual measures for the treatment of cardiogenic pulmonary edema are merely palliative and temporizing. Relief of the pulmonary edema was effectively achieved only in Case 3, where prompt decompression of the intracranial pressure was carried out. This patient was the only survivor, although Cases 1, 5, 7, and 10 had potentially reversible neurological processes.

In cases of acute pulmonary edema where reversal of the central nervous system disease is felt to be possible, positive endotracheal respiratory assistance should be instituted for the period of time necessary to perform the most expedient intracranial decompression.

Summary

We have reported 11 patients, ages 12 to 44, without primary cardiopulmonary disease who developed severe acute pulmonary edema in response to some lesion of the central nervous system. Increased intracranial pressure appeared to be the only common etiological factor. The pulmonary edema appeared suddenly within 2 hours after elevation of intracranial pressure. In spite of supportive, palliative, and operative measures, 10 of these 11 patients died. The autopsies in each case showed severe pulmonary congestion and moderately diffuse cerebral edema.

Permanent relief of the pulmonary edema depends on reduction of intracranial pressure. Other measures proved to be only palliative and temporary; the most important of these was endotracheal positive-pressure respiration.

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