

Legionnaire's disease associated with acute respiratory distress syndrome and acute cerebral oedema

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Abstract

Objective: To report the original observation of a patient with legionella's pneumopathy complicated with acute respiratory distress syndrome (ARDS) and a concomitant cerebral oedema occurred in the setting of positive end-expiratory pressure, reversible with the weaning of mechanical ventilation.

Design and Setting: Case report, Intensive Care Unit, General Hospital.

Patient: Young female patient with HIV infection

Interventions: Diagnostic fiberoptic bronchoscopy, legionella urinary antigen, lumbar puncture, computed tomography and magnetic resonance imaging of the brain, mechanical ventilation, positive end-expiratory pressure, low tidal volume, permissive hypercapnia, prone position, systemic antibiotherapy.

Results: Cerebrospinal fluid polymerase chain reaction was negative for both legionella and herpes

virus or any other opportunistic infection. Chest radiographies showed the progressive resolution of ARDS with adapted antibiotherapy. The clinical improvement and total reversibility of cerebral oedema were observed in magnetic resonance imaging of the brain with concomitant weaning of positive end-expiratory pressure and mechanical ventilation.

Conclusion: In ARDS, protective ventilatory strategy using low tidal volume ventilation, positive end-expiratory pressure and permissive hypercapnia are recommended to improve intrapulmonary shunt, arterial oxygenation and to decrease mortality, but the incidence of neurological complications as intracranial hypertension is probably underestimated. Further studies to evaluate the neurological impact (hemodynamic and anatomical consequences) of mechanical ventilation in ARDS are necessary.

Keywords: Acute respiratory distress syndrome; legionella; hiv infection; cerebral oedema; intracerebral pressure; permissive hypercapnia; positive end-expiratory pressure; prone position.

Introduction

The most appropriate treatment of acute respiratory distress syndrome (ARDS) include a protective ventilatory strategy using low tidal volume ventilation and positive end-expiratory pressure (PEEP) [1]. The main objective

of this recommended approach is to reduce mortality, by achieving adequate arterial oxygenation, reducing intrapulmonary shunt and protecting the lung from injurious mechanical forces that occur from ventilation, which is finally the rationale of « permissive hypercapnia » [2,3]. Studies on experimental acute lung injury (ALI) and humans with ALI/ARDS also demonstrated reductions in inflammatory cytokines in the alveolar lavage fluid and plasma when higher PEEP was used. An alternative approach including prone positioning has also been proposed, but has not yet proved beneficial [1]. However, hemodynamic effects of PEEP included increased intrathoracic pressure leading to reduced venous return, decreased cardiac output and increased intracerebral pressure [4]. We report the original observation of a legionella's pneumopathy with concomitant ARDS and

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cerebral oedema occurring in the setting of mechanical ventilation including PEEP and permissive hypercapnia. The clinical improvement and total reversibility of cerebral oedema with concomitant weaning of mechanical ventilation may discuss the neurological impact and consequences in non injured brain of permissive hypercapnia and PEEP.

Case Report

A 42-year-old Caucasian woman was admitted in our intensive care unit in September 2003, suffering from an acute respiratory distress syndrome with dyspnea, fever and myalgia developed over the previous days. She had an HIV infection since 1987 (no drug abuse, sexual transmission). The CD4 cells counts was $910/\text{mm}^3$ and viral charge was 16000 copy/ml, and she had stopped her anti-retroviral treatment since September 2001. She had, until then, never presented opportunistic infection. At admission (J1), physical examination revealed cyanosis, respiratory rate 28/m, pulse rate 110/m, temperature 39°C , weight 64 kg without oedema, blood pressure 115/65 mmHg, bilateral ronchi, no hepato-splenomegaly, few inguinal ganglions, consciousness was normal, Glasgow coma scale 15, neurological examination was not focal and there was no neck rigidity. Chest radiography showed bilateral alveolar infiltrates (**Figure 1**). Electrocardiogram revealed sinus tachycardia. Arterial gazometry showed at 21% FiO_2 : ph 7.48, PO_2 54 mmHg, PCO_2 30 mmHg, saturation 86%. Biological data were: leukocytes 700/



FIGURE 1. CHEST RADIOGRAPHY : BILATERAL ALVEOLAR INFILTRATES, LEGIONNAIRE'S DISEASE ASSOCIATED WITH ARDS.

ml, fibrinogen 7.5 g/l, C-reactive protein 32 mg/l, procalcitonin 6 ng/ml, hyponatremia 132 mmol/l, creatinin 100 mmol/l, mild elevation of transaminases; coagulation profile and other blood counts were normal. Non-invasive ventilation was quickly started to obtain a $\text{SpO}_2 = 93\%$, but it was necessary to intubate this non participating and worsened patient with ARDS ($\text{PaO}_2/\text{FiO}_2 < 100$). Mechanical ventilation strategy included low tidal volume (6ml/kg, $\text{Vt}=380\text{ml}$), PEEP 20 cmH_2O in supine position, and PEEP 15 cmH_2O in prone positioning (16h per day). Sedation was obtained with the continuous combination of midazolam, fentanyl and cisatracurium besilate.

The diagnosis of Legionella pneumonia was made on fiberoptic bronchoscopy with bronchoalveolar lavage (positive direct fluorescent antibody) and urinary antigen assay for Legionella pneumophila serogroup 5-6. Bronchoalveolar lavage was negative for any other bacteria, viruses or fungi. Hemocultures were all negative and serologic identification confirmed later the diagnosis of legionnaire's disease. Systemic antibiotherapy with rovamycin and ofloxacin was immediately initiated. Glucocorticoids 1mg/kg were administered at J7, while apyrexia was obtained 3 days before. Transoesophageal echocardiogram was normal and showed no endocarditis.

At J8, while mechanical ventilation with PEEP 15 cmH_2O and permissive hypercapnia were going on, transaminases remained at the upper limit of normal and physical examination and abdominal echography showed a recent hepato-splenomegaly. Arterial gazometry ($\text{FiO}_2=50\%$) was: pH=7.29 $\text{PO}_2=78$ mmHg, $\text{PCO}_2=59$ mmHg, bicarbonates=38, saturation=97%. At J10, clinical and gazometric ($\text{FiO}_2/\text{PaO}_2 > 250$) improvement, and chest radiography allowed the weaning of the sedation and the beginning of a gradual withdrawal of mechanical ventilation. Tidal volumes were increased to 10 ml/kg (610 ml) and PEEP was decreased to 5 cmH_2O , prone position was also stopped.

Two days later (J12), the patient remained apyretic, hemodynamic parameters were normal, but waking up was not adapted with Glasgow coma scale 10. Physical examination was not focal and no seizure was observed. Renal function was normal and midazolam was not detected in the serum. There was no metabolic disorder, particularly normal natremia, CRP was 6 mg/l. Arterial gazometry ($\text{FiO}_2=30\%$) was: pH=7.38, $\text{PO}_2=82$ mmHg, $\text{PCO}_2=41$ mmHg, saturation 98 %. A computed tomography of the head showed a major cerebral oedema with intracranial hypertension, no displacement of median structures, diffuse hyperemia and leptomenigeal enhancement (**Figure 2**). Electroencephalogram showed a non-specific cerebral sufferance but no sign for an un-

recognized or “silent” seizure. Rifampicin and acyclovir were added to rovamycin and ofloxacin. Systematic intravenous fosphenytoin and mannitol were started. Positive end- expiratory pressure was totally stopped. The



FIGURE 2. COMPUTED TOMOGRAPHY OF THE BRAIN (J12): CEREBRAL OEDEMA, DIFFUSE HYPERHEMIC AND LEPTOMENINGEAL ENHANCEMENT.

main biological data over time with the timing of neurological deterioration, CTs and ventilator parameters are resumed in **Table 1**. Lumbar puncture was made and cerebrospinal fluid was strictly normal (spinal/serum glucose= 0.9, protein= 0.1 g/l, WBC count = 0). The initial opening pressure recorded during the lumbar puncture was 800 mmH₂O. Unfortunately, intracranial pressure could not be monitored during the further evolution. The polymerase chain reaction for JC virus, p24 antigen, parvovirus, herpes virus 1 and 2, and legionella were all negative, cryptococcal meningitis was also excluded by india ink staining. So, the diagnosis of meningoencephalitis was unlikely and treatment with acyclovir and rifampicine was stopped at J14. At J16, a computed tomography of the brain showed an improvement of the cerebral oedema. Four days later (J19), the patient was extubated, afebrile, neurological examination was normal and hepatosplenomegaly had totally removed. Chest radiographies confirmed the progressive resolution of bilateral infiltrates. Arterial gazometry (O₂=31/m) was: ph=7.38, PO₂=74 mmHg, PCO₂=36 mmHg, saturation 95%. Both computed tomography and magnetic resonance imaging of the brain (J20) were strictly normal (**Figure 3**). The patient received a total of 21 days of rovamycin and ofloxacin and was discharged home after 33 days of hospitalisation.

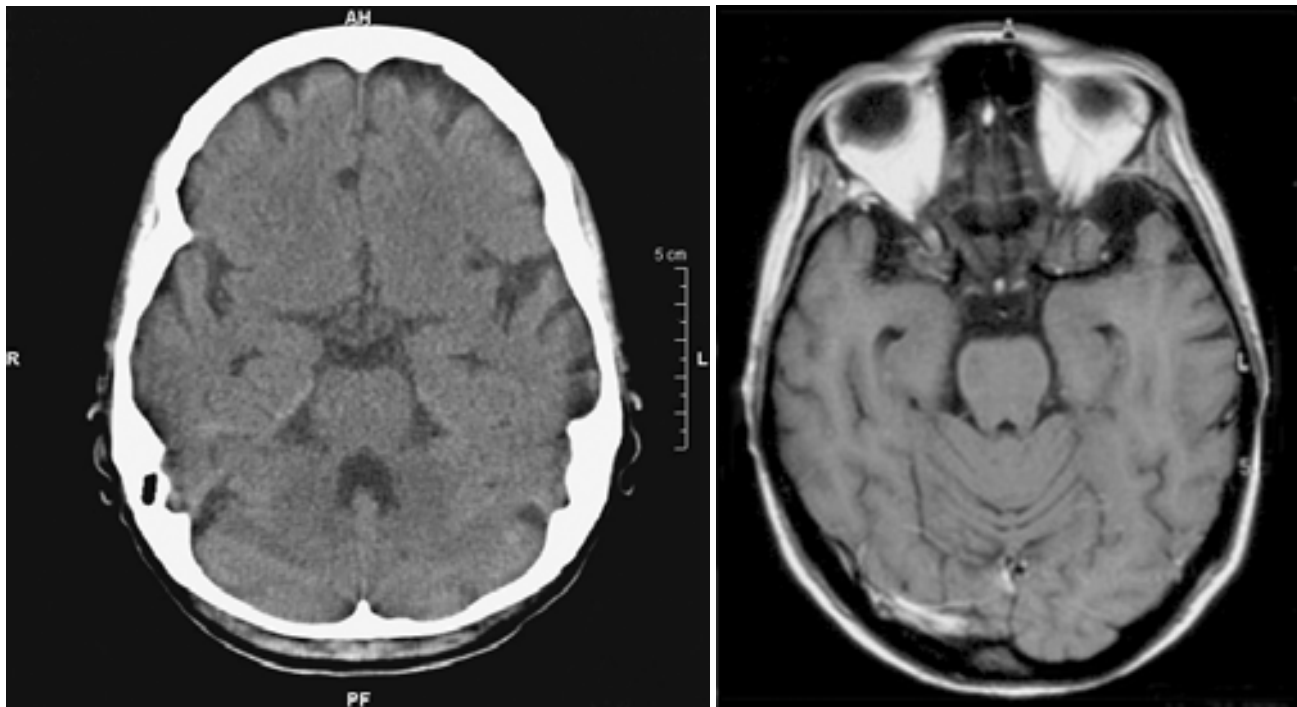


FIGURE 3. CT-SCAN AND MAGNETIC RESONANCE IMAGING OF THE BRAIN (J20) : TOTAL REVERSIBILITY OF THE CEREBRAL OEDEMA 8 DAYS AFTER THE WEANING OF MECHANICAL VENTILATION INCLUDING PERMISSIVE HYPERCAPNIA AND POSITIVE END-EXPIRATORY PRESSURE.

TABLE 1. BIOLOGICAL DATA WITH THE TIMING OF NEUROLOGICAL DETERIORATION, CT-SCAN AND VENTILATOR PARAMETERS.

	J1	J8	J10	J12	J16	J20	
Clinical presentation	Admission	Intubation				(Extubation J19)	
• Temperature (°C)	39	38.7	37.9	37.4	37.2	36.9	37.3
• Mean Arterial pressure (mmHg, no inotropic support)	84	80	81	86	84	76	79
• Glasgow goal score	15	-	-	-	10	15	15
Arterial gazometry							
• PaO ₂ (mmHg)	54	65	78	85	82	90	82
• PCO ₂ (mmHg)	30	43	59	62	41	43	38
• pH	7.48	7.33	7.29	7.25	7.39	7.42	7.4
• PaO ₂ /FIO ₂	250	<81	158	267	276	441	410
• Sat (%)	86	93	97	98	100	100	100
Sedation	-	+	+	+	-	-	-
Ventilator parameters							
• PEEP (cmH ₂ O)	-	15-20	15	5	5	0	-
• Vt (ml/kg)	-	6	6	10	10.5	10	-
Prone position (16h/day)	-	-	+	+	-	-	-
Other biological data							
• Natremia (mmol/l)	128	136	138	137	142	142	140
• CRP (mg/l)	32	25	13	6	3	3	2.5
• WBC (/ml)	700	1050	1100	950	850	850	870
Lumbar puncture							
Count cell	-	-	-	Normal	-	-	-
Opening pressure				800mmH ₂ O			
EEG	-	-	No seizure	No seizure	-	-	-
Brain CT-Scan	-	-	-	Cerebral oedema (fig2)	Improvement	Normal (fig3)	
Brain MRI	-	-	-	-	-	Normal (fig3)	

Discussion

We describe here the case report of an ARDS and legionella pneumopathy with cerebral oedema occurring in the setting of permissive hypercapnia and positive end-expiratory pressure. In this original observation, we provide many clinical findings which are suggestive for a correlation between ventilator settings and the occurrence of significant cerebral oedema, reversible with the weaning of mechanical ventilation.

The Legionella pneumophila is recognised in most studies as a common cause of severe acquired community pneumonia. SAPS II score and intubation requirement are associated with a higher mortality, whereas the administration of an appropriate antibiotherapy (quinolone or macrolide) within 8 h of ICU arrival leads

to better survival [5]. The pulmonary complications of legionnaire's disease are more frequent in HIV infection, with a prevalence of respiratory failure and ARDS in 46 to 75%, and related mortality of 15% [6]. The most appropriate method of mechanical ventilation in ARDS has been controversial since the syndrome was first described. Current recommendations are a supportive treatment with low tidal volume ventilation and positive end-expiratory pressure, to avoid ventilator-associated lung injury from overdistension and to reduce mortality [1,2]. Prone positioning has also been proposed, leading to substantial improvement in arterial oxygenation in approximately 65% of ARDS patients, but though this method can reduce requirement for PEEP and FiO₂, it has not yet been proved to be associated with survival benefits [1,7]. The effects of such positive pressure ventilation on pulmo-

nary and cardiac hemodynamic are well described in experimental models and human studies [1]. Nevertheless, this strategy may also be associated to neurological complications related with increased intracranial pressure (ICP). These neurological effects are not well studied. Theoretically, PEEP leads to increased intrathoracic pressure which in turn reduces venous return, increases cerebral venous pressure, increases ICP and decreases mean arterial pressure. Another important consequence of low tidal volume is an unintentional or « permissive » hypercapnia and acidosis which could have important consequences on cerebral hemodynamic. Indeed, an acute increase of PCO_2 can lead to increased cerebral blood flow and ICP [4].

In this observation, relationship between cerebral oedema and permissive hypercapnia, decreased pH and high PEEP could be suggestive and may discuss the neurological monitoring in patients with ARDS and ventilator parameters strategy. Indeed, we observed a total improvement of cerebral oedema four days after the weaning of PEEP, and decrease of $PaCO_2$ (see table 1). In the same time, there was no argument for another cause of intracranial hypertension such as meningoencephalitis or uncontrolled sepsis, intracerebral infarction or hemorrhage, thrombosed dural sinuses, hydrocephalia, systemic hypotension, cardiac arrest, coagulopathy, acute metabolic disorder or SIADH, lactic acidosis, silent seizure, or traumatic head injury. A cytotoxic and ischemic oedema due to detrimental effect of hypoxemia then hypoxia could be discussed too, with SaO_2 (saturation O_2) and PaO_2 which were quite substantial at the admission, but these parameters quickly improved with adequate therapeutic measures, to obtain a PaO_2 in the normal range. Prone position (16h per days from J2 to J10), can lead to increased intra-abdominal and intrathoracic pressure reduces venous return and then increases ICP too [8,9].

In this young HIV patient, the case of a combined ARDS, legionella pneumopathy and cerebral edema first pointed to an acute encephalitis, either as neurological manifestation of disseminated legionella's disease or as complication of AIDS [10]. This hypothesis was ruled out with a normal lumbar puncture and the negativity of cerebrospinal fluid polymerase chain reaction for herpes virus, JC virus, parvovirus, p24 antigen and legionella. Any other opportunistic infection was excluded too. The EEG showed no sign for an unrecognized or "silent" seizure without clinical convulsions. At last, clinical improvement and total reversibility of this cerebral oedema was observed in computed tomography and magnetic resonance imaging of the brain with concomitant weaning of positive end-expiratory pressure and mechanical ventilation. About the hepatosplenomegaly occurred dur-

ing the setting of positive end-expiratory pressure, it quickly disappeared with the weaning of mechanical ventilation too, leading to the hypothesis of the effect of PEEP and/or prone position on intra-abdominal pressure and ICP [11,12]. This observation may also simply reflect the normal evolution of the disease, but the correlated chronology of both apparition and resolution of splenomegaly with the mode of mechanical ventilation with or without PEEP is quite disconcerting.

The influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in patients with acute stroke or traumatic brain injury is well described. In these patients, a strategy to increase PEEP from 4 to 12 cmH_2O seems to be safe and not associated with increased ICP or decreased cerebral perfusion [13,14]. In a recent study, Videtta et al demonstrated that 15 cmH_2O PEEP produced a small but significant increase in ICP but no change in cerebral perfusion pressure [15]. Nevertheless, clinicians are very scrupulous in this context of brain injury, with very careful intracranial pressure monitoring. The situation is quite different in ARDS or in non-traumatic patients. Indeed in ARDS, the main interest results in the ventilation strategy which includes much higher levels of PEEP, and more recently alveolar recruitment manoeuvres [1]. Experimental studies in rats demonstrated that cerebral water content increased with hypercapnia and hypoxia [16,17]. Feldman et al also demonstrated that PEEP of 10 $cm H_2O$ reduced intracranial compliance in the rabbit model [18]. Acute hypercapnia in ewes induced a significant increase in intracranial pressure, which can be attenuated by correction of blood pH with the administration of sodium bicarbonates [19]. In patients with initially normal intracranial pressure, PEEP at 10 and 15 $cm H_2O$ significantly increased ICP but the clinical relevance was questionable because the authors did not observe any change in cerebral perfusion pressure [20]. Kolbitsch et al showed the impact of increased mean airway pressure on cerebral perfusion evaluated with contrast-enhanced MRI. They demonstrated a significant reduced regional blood flow and increased regional mean transit time and cerebrovascular resistance in healthy volunteers using 12 $cm H_2O$ CPAP [21]. In a very recent study, Scala et al showed in healthy adult humans the decrease of cerebral blood flow velocity when incremental levels of continuous positive airway pressure were delivered [22]. Tasker et al describe a patient with meningitis, cerebral oedema and ARDS in whom the impact of hypercapnia and PEEP 10 cmH_2O is suspected on increased intracerebral pressure and cerebral hyperemia, leading to the very pertinent question « how permissive can hypercapnia be? » [23,24]. Neurological complications of prone position are not known but there

is evidence that the elevation of intra-abdominal pressure leads to elevation of intracranial pressure [8]. Finally, the question of the way of weaning from mechanical ventilation and permissive hypercapnia is also relevant. A recent study demonstrated that an inadvertent decrease in arterial CO₂ may leads to a decline of cerebral blood flow and a consequent potential for producing brain ischemia [25].

In summary, if low tidal volume, positive-end expiratory pressure and permissive hypercapnia are the most appropriate ventilation strategy in ARDS, neurological consequences and increased ICP in non injured brain are not known yet. In our opinion, the incidence of these neurological complications is probably underestimated, due

partly to the inherent difficulty in neurological monitoring of sedated patients. Further studies, including non invasive methods (cerebral blood flow velocity measurement with systematic transcranial Doppler, coupled with computed tomography or magnetic resonance imaging of the brain) seem necessary to evaluate the potential neurological complications in the course of mechanical ventilation in ARDS survivors.

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