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Intracranial pressure and cerebral perfusion pressure in experimental *streptococcus pneumoniae* meningitis

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Summary. Clinical studies have demonstrated the prognostic importance of increased intracranial pressure in central nervous system infections. To delineate development of intracranial pressure in meningitis experiments were carried out in rabbits. Meningitis was induced by injecting *streptococcus pneumoniae* bacteria into the cisterna magna and blood, and intracranial pressures were continuously recorded. In the experimental model, three stages were seen: incubation period (0–8 h) – in which CSF becomes positive for the infecting organism and biochemical changes occur, but there are no hemodynamic or intracranial pressure changes; stage of slowly increasing intracranial pressure – because blood pressure remains normal, cerebral perfusion pressure is maintained adequate for cerebral metabolic need (9–24 h); terminal stage (> 25 h) – with hemodynamic collapse, critical reduction of cerebral perfusion pressure, cerebral ischemia, and death of the experimental animals. It is suggested that a similar sequence occurs in human disease. The clinical implication stresses the need for early recognition and treatment of intracranial hypertension as an important adjunct to antibiotic treatment of the infecting organism.

Key words: Meningitis-experimental – Intracranial pressure – Cerebral perfusion pressure – *Streptococcus pneumoniae*

Introduction

Intracranial hypertension often complicates severe central-nervous-system (CNS) infections [4]. With concurrent loss of cerebral autoregulatory function, such increase in intracranial pressure (ICP) might greatly reduce cerebral perfusion pressure (CPP), which is calculated as the difference between mean arterial blood pressure (MABP) and ICP. Such reduction in CPP might cause cerebral ischemia by diminishing cerebral blood flow (CBF) [10], becoming a significant factor in the prognosis of infants and children with CNS disease [9].

It thus becomes important to delineate the temporal changes in ICP during CNS infections. This will further understanding of the pathophysiology of brain damage in these diseases and might direct therapeutic endeavors to prevent such damage.

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A study of ICP and CPP in an experimental model of meningitis in the rabbit is reported.

Materials and methods

Experiments were performed in adult rabbits weighing 2.5–4 kg.

Surgical preparation

The rabbits were anesthetized by intravenous injection of phenobarbital sodium (30 mg/kg). In the anesthetized animal, femoral vein (for administrating fluids and drugs) and artery (for continuously monitoring MABP and blood sampling for blood gases, biochemistry, and acid base balance) were canulated.

Through a burr hole drilled in the fronto-parietal region of the skull, a subdural catheter was inserted for continuously monitoring ICP. The MABP and ICP canulae were connected via non-compliant extension tubes to pressure transducers and the MABP and ICP were continuously displayed and recorded on a multichannel recorder. CPP was calculated from these values. After tracheostomy was performed, the rabbits were paralyzed with pancuronium bromide (0.1 mg/kg) and artificially ventilated with a tidal volume of 10 ml/kg at a rate, as required, to maintain normal PCO_2 (37–42 mm Hg) and PO_2 (> 80 mm Hg). Repeated doses of phenobarbital sodium and pancuronium bromide were administered throughout the experiment to prevent spontaneous movement and respiration. Normothermia was maintained with a heating lamp and acidoses corrected, as necessary, with sodium bicarbonate.

Experimental protocol

During all experiments the rabbits were infused with an electrolyte/glucose solution to maintain hydration and blood-glucose level. Repeated blood samples were drawn to examine electrolytes, glucose, blood gases, and acid base balance. Infused solutions and ventilator settings were changed, as necessary, to maintain normal values.

Control animals

In five rabbits, killed bacteria were injected into the cisterna magna. The rabbits were then surgically prepared, as above, and MABP and ICP continuously monitored for 10–14 h. A CSF sample was then withdrawn for analysis. Afterwards, all canulae were removed and surgical wounds sutured. The animals were allowed to regain full consciousness and spontaneous respiration. They were then returned to their cages for long-term observation.

Preliminary experiments

Immediately after surgical preparation of ten animals, as above, the cisterna magna was percutaneously punctured. Then cerebrospinal fluid (CSF) was withdrawn to control bacterial cultures and cell count and determine glucose and protein levels, and a bacterial inoculum of 0.7 ml *Streptococcus pneumoniae* was slowly injected at a final concentration of 10^7/ml. Thereafter, CSF was withdrawn every hour for glucose and protein determinations, cell count, and culture. Animals were maintained and monitored, as above, until death.

Experimental animals

After inducting meningitis, 20 animals were returned to their cages. According to the results of the preliminary experiments and in order to avoid the need for extremely prolonged continuous monitoring, the animals were divided into two groups:

Group I

Surgical preparation was undertaken 10–12 h after inducting meningitis, as above. At this time, a single CSF examination was performed. Animals were then monitored until death.

Group II

Surgical preparation was undertaken 18–22 h after inducting meningitis. Animals were then continuously monitored until death.

Results

Control animals

In rabbits injected with killed bacteria, CSF remained normal and cultures sterile. During up to 14 h of continuous monitoring, MABP and ICP remained unchanged from control pressures.

The animals continued, on long-term follow up, to exhibit no clinical signs of CNS involvement (see below) and no deaths occurred.

Preliminary experiments

Between 2 h and 4 h after inducting meningitis, CSF cultures became positive for the infecting organism and pleocytosis occurred, reaching values of 18000/mm^3 after 10–12 h. Concomitant fall in CSF glucose (0–1.7 mmol/l) and increase in protein (> 2000 mg/l) were noted.

Group I

At 10–12 h after inoculation of the infecting organism, prior to anesthesia and surgical preparation, the rabbits showed signs of CNS involvement: hyperthermia, lethargy, ataxia, hyperreflexia, and hypoventilation.

Group II

At 18–22 h, these animals displayed signs of severe CNS infection: hypothermia, opisthotonus, hyporeflexia, and rapid shallow respirations.

MABP and ICP data are summarized in Fig. 1: control MABP was 82 ± 1.6 mm Hg ($X \pm$ SEM). MABP remained essentially unchanged from control levels during the first 24 h after inducting meningitis. However, after 20 h, progressively greater variance in MABP occurred between animals: 75.5 ± 5.0 mm Hg at 21 h and 72.4 ± 9.7 mm Hg at 24 h. At 30 h MABP was significantly ($P < 0.001$) lower than control levels, reaching pressures of 65.0 ± 5.9 mm Hg.

Control ICP was 4.8 ± 0.2 mm Hg. Between 4 h and 6 h after bacteria were injected into the cisterna magna, ICP began to rise. ICP became significantly ($P < 0.001$) different from control after 8–12 h at pressures of 9.3 ± 0.8 mm Hg.

Thereafter, ICP continued to rise rapidly, reaching levels of 16.9 ± 4.5 mm Hg at 16 h, 27.1 ± 6.9 mm Hg at 20 h, and 36.4 ± 3.0 mm Hg at 25 h (range 18–79 mm Hg). Because MABP remained unchanged for the first 24 h concurrent with the increase in ICP, CPP slowly deteriorated from control values of 77 ± 1.5 mm Hg to 36.0 ± 3.7 mm Hg at 25 h. During the first 20–25 h of the experiment, bivariate analysis showed independence of ICP from MABP, signifying normal autoregulatory function. With loss of autoregulation, ICP became progressively dependent on MABP. Although the animals showed marked variation in MABP and ICP, at this stage of the experiment all started to deteriorate hemodynamically, exhibiting falling blood pressure and development of intractable acidosis unresponsive to multiple doses of bicarbonate. Attempts to maintain normal

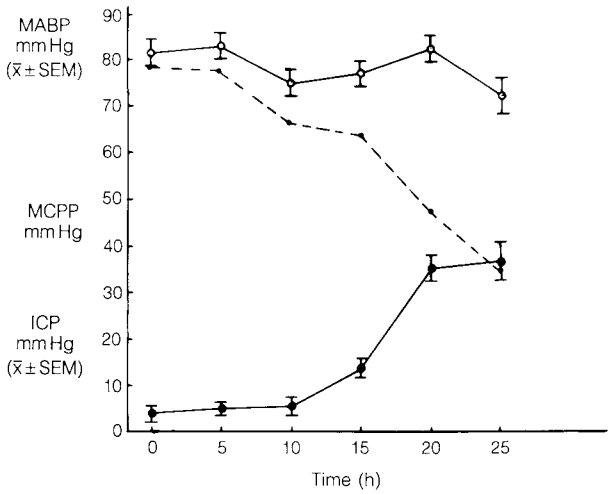

Fig. 1. Mean arterial blood pressure, cerebral perfusion pressure, and intracranial pressure in experimental meningitis

blood pressure with increasing dosage of dopamin infusion failed. The parallel increase of ICP with decreasing MABP caused a fall in CPP, which remained below 35 mm Hg. Brain ischemia became clinically evident, with the appearance of widely dilated, nonreactive pupils and disappearance of spontaneous movement and respiration (without further anesthesia and paralysis). All animals died shortly after these hemodynamic and clinical changes occurred.

Discussion

Central nervous system infections of infancy and childhood still carry a high mortality and morbidity [1, 11] despite earlier diagnosis, more effective antibiotic protocols, and improved intensive care facilities. Therapeutic failures have been attributed to delayed recognition of the disease, poor penetration of antibiotics into the CNS, and development of brain edema. The brain is situated in a "closed box" (except in the infant with an open fontanel) and the pressure inside the skull (ICP) is dependent on the volume of its three major components: brain tissue, CSF compartment, and vascular compartment [6]. According to the Monroe-Kelly doctrine, an increase in the volume of one intracranial component must be reciprocally accompanied by a reduction in the volume of another component or intracranial hypertension will develop. Increase of brain water during infection may be partially compensated by brain-tissue compliance, shift of ventricular CSF to the spinal compartment, and changes in production and reabsorption of CSF [2]. These defence mechanisms, however, are very limited. During severe infection, with reduction of brain compliance, brain edema and the accompanying increased ICP may cause brain damage over and above the deleterious effects of the infection itself by producing acute herniation [5] and by reducing CBF [2]. In the normal brain, an increase in ICP may be further compensated by parallel increase in blood pressure (Cushing effect), thus maintaining adequate CPP. In severe infections of the CNS, however, circulatory collapse often supervenes with resultant fall in CPP.

Table 1. Stages in development of experimental meningitis

Stage	Incubation period 0–8 h	Progressive disease 9–22 h	Terminal disease > 23 h
Finding			
Leukocytes	> 500 mm^3	18000 mm^3	
Glucose	Reduced	0–1.7 mmol/l	
Protein	Increased	> 2000 mg/l	
Clinical and neurologic findings	Hyperreflexia Hyperpyrexia Lethargy Ataxia Hypoventilation	Hyporeflexia Hypothermia Opistotonus Hyperventilation	Death of animal
MABP	82 ± 1.6 mm Hg	75.5 ± 5 mm Hg	65 ± 5.9 mm Hg
MICP	4.8 ± 0.2 mm Hg	16.9 ± 4.5 mm Hg	36.4 ± 3 mm Hg
MCPP	77 ± 1.5 mm Hg	36 ± 3.7 mm Hg	< 30 mm Hg

MABP, mean arterial blood pressure; MICP, mean intracranial pressure; MCPP, mean cerebral perfusion pressure

Loss of cerebral autoregulatory function in these diseases prevents normal maintenance of CBF, which becomes directly dependent on CPP. The reduction of CPP below crucial levels may, by causing brain ischemia, become a dominant factor in the prognosis of CNS infections.

Although the mode of infection in our experimental model does not mimic clinical disease [7, 8], it is suggested that the sequence of events in the CNS resembles meningitis in humans once the bacteria have penetrated into the CSF compartment.

Data from the present study suggest that three stages occur in the natural history of untreated meningitis (Table 1):

Stage I: 0–8 h after bacteria are introduced into the CNS

During this incubation period, CSF becomes positive for the infecting organism, pleocytosis develops, glucose decreases, and protein increases. ICP begins to rise, but there is no clinical neurologic evidence of CNS disease. It is difficult to estimate the length of this period in human disease, because no clear-cut signs of CNS involvement are present and symtoms might be general and inadequate to make the correct diagnosis.

Stage II: 9–25 h

During this stage, the disease rapidly progresses as demonstrated in the experimental model by deteriorating neurological status and increased ICP. Blood pressure, however, is maintained and cerebral autoregulatory function remains intact, as evidenced by independence of ICP from MABP. CPP slowly decreases, but apparently remains adequate (above 30 mm Hg) to maintain CBF sufficient for metabolic demand, thereby preventing cerebral ischemia. This is probably

the most crucial period of the disease, because early recognition might enable initiation of treatment modalities before brain compliance and cerebral autoregulatory function are lost, thereby interrupting the natural course of untreated meningitis.

Stage III: more than 25 h

At this stage, hemodynamic collapse supervenes with resultant fall of blood pressure, failing cerebral autoregulatory function, and decreasing CPP. At this stage, CPP falls to levels inadequate to maintain sufficient CBF for metabolic demand and cerebral ischemia occurs. The disease is no longer amenable to treatment, as evident by inability to maintain blood pressure with vasoactive drugs and combat the severely intractable acidosis. In the experimental model, resultant brain damage inevitably leads in the experimental model to death of the animals. This stresses the importance of treating both the infecting organism and the hemodynamic aberrations in human disease, early enough to prevent progression to the stage where they are no longer amenable to treatment.

Conclusions

It is suggested that results of this study might have several clinical implications:

1. Increased ICP develops early in CNS infections.
2. Continuous monitoring of blood pressure and ICP in severe CNS infections to enable early identification of reduced blood pressure and intracranial hypertension might be of crucial importance in the clinical management of these patients.
3. Such monitoring will enable early initiation of treatment directed at maintaining blood pressure, reducing ICP, and thereby maintaining CPP adequate to maintain CBF.
4. Treatment of intracranial pressure might be an important adjunct to antibiotic medication in reducing mortality and morbidity in CNS infections.

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