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Patterns of cerebral tissue oxygen tension and cytoplasmic redox state in bacterial meningitis

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Key Words

Bacterial meningitis; Intracerebral microdialysis; Cerebral tissue oxygenation; Intracranial pressure Ischemia; Mitochondrial dysfunction.

Abstract

Background: Compromised cerebral energy metabolism is common in patients with bacterial meningitis. In this study simultaneous measurements of cerebral oxygen tension and lactate/pyruvate ratio were compared to explore whether disturbed energy metabolism was usually caused by insufficient tissue oxygenation or compromised oxidative metabolism of pyruvate indicating mitochondrial dysfunction.

Subject and Methods: Ten consecutive patients with severe streptococcus meningitis were included in this prospective cohort study. Intracranial pressure, brain tissue oxygen tension ($PbtO_2$) and energy metabolism (intracerebral microdialysis) were continuously monitored in nine patients. A cerebral lactate/pyruvate (LP) ratio <30 was considered indicating normal oxidative metabolism, LP ratio >30 simultaneously with pyruvate below lower normal level (70 µmol/L) was interpreted as biochemical indication of ischemia, and LP ratio >30 simultaneously with a normal or increased level of pyruvate was interpreted as mitochondrial dysfunction. The biochemical variables were compared with $PbtO_2$ simultaneously monitored within the same cerebral region.

Results: In two cases the LP ratio was normal during the whole study period and the simultaneously monitored $PbtO_2$ was 18 ± 6 mmHg. In 6 cases, interpreted as mitochondrial dysfunction, the simultaneously monitored $PbtO_2$ was 20 ± 6 mmHg and without correlation to the LP ratio. In one patient, exhibiting a pattern interpreted as ischemia, $PbtO_2$ decreased below 10 mmHg and a correlation between LP and $PbtO_2$ was observed.

Conclusion: This study demonstrated that compromised cerebral energy metabolism, evidenced by increased LP ratio, was common in patients with severe bacterial meningitis while not related to insufficient tissue oxygenation.

Editorial Comment

In a cohort of patients with streptococcal meningitis, a predominant pattern of cerebral mitochondrial dysfunction rather than insufficient oxygenation was demonstrated using multimodal neuromonitoring. This study highlights the potential for multimodal neuromonitoring to investigate pathology, guide treatment, and design interventional trials in patients with acute cerebral dysfunction.

Introduction

Despite adequate antibiotic therapy mortality has remained high in community-acquired bacterial meningitis (20-30%).[1-5] Elevated intracranial pressure (ICP) appears to be an important cause of unfavorable outcome[6, 7] as increased ICP may result in a decrease in cerebral perfusion pressure (CPP), a reduction of cerebral blood flow and compromised energy metabolism. In a recent retrospective study of patients with severe bacterial meningitis we demonstrated that cerebral oxidative metabolism was affected in approximately 50% of the cases.[8] Based on the fact that a similar biochemical pattern was obtained in experimental, cyanide induced mitochondrial dysfunction[9] it was tentatively suggested that bacterial meningitis might impair mitochondrial function. A recent experimental study of lipopolysaccharide (molecule from outer membrane of gram-negative bacteria) induced aseptic meningitis supported this interpretation.[10] Further, similar biochemical patterns have been interpreted as indicating mitochondrial dysfunction in various severe neurosurgical conditions.[11-12]

The present investigation had two primary objectives: Firstly, to verify in a prospective study that cerebral energy metabolism is frequently impaired in severe bacterial meningitis; secondly, to examine whether it is correct to separate the diagnosis of cerebral ischemia from mitochondrial dysfunction based on the biochemical pattern obtained during intracerebral microdialysis. In the present study we relate data from measurements of brain tissue oxygen tension ($PbtO_2$) to simultaneously recorded data reflecting cerebral cytoplasmic redox state evaluated from cerebral interstitial lactate/pyruvate (LP) ratio obtained by microdialysis. In cerebral ischemia the reduction of cerebral blood flow will decrease $PbtO_2$ and cause an instantaneous increase of the LP ratio.[13, 14] In mitochondrial dysfunction an increase in LP ratio has been shown to occur at an unchanged $PbtO_2$.[9, 15] As knowledge regarding the relations between LP ratio and $PbtO_2$ remains incomplete[16] the present study may be of relevance not only for patients with severe bacterial meningitis but also for the understanding in general of data obtained during cerebral multi-modal monitoring.[a]

Materials and Methods

Study population

[a] Preliminary data has been presented as a poster at the 34th annual meeting of NSCMID 2017, Faroe Islands.

Consecutive patients with severe community-acquired bacterial meningitis complying with the inclusion criteria below and admitted to the department of Infectious Diseases, Odense University Hospital, Denmark during the period January 2014 to June 2016.

Management Protocol.

The project was carried out according to the 1964 Declaration of Helsinki and approved by the national ethics committee (no. 1302047) and the Danish data agency (no. 2012-58-0018/2008-58-0035). It is categorized as an 'urgent' project where surrogate informed consent could be obtained after the patient´s inclusion in the project. Patient informed consent was obtained when the individual was able to decide on the participation.

Inclusion criteria were:

1. Age ≥ 18 years

2. Confirmed community-acquired bacterial meningitis with positive cerebrospinal fluid (CSF) microscopy/culture or high clinical suspicion of meningitis with increased CSF cell count and/or decreased CSF/blood glucose ratio.

3. Decreasing Glasgow Coma Scale (GCS) < 9 and candidate for ICP monitoring.

4. Admission to the intensive care department.

No patients were excluded after inclusion in the study and no adverse events due to intracerebral monitoring and use of microdialysis probes were seen. In one patient (Pat. 2) the microdialysis catheter malfunctioned and replacement was possible.

The neurosurgeon on call evaluated the need for ICP monitoring and inserted a triple lumen bolt (Integra Neurosciences Ltd. New Jersey, USA) into the right frontal lobe for positioning of all three intracerebral probes.

All patients received antibiotics according to current guidelines (ceftriaxone + penicillin/ampicillin, or meropenem) and subsequently adapted to resistance tests. Corticosteroids were given according to guidelines that is, before or concomitantly with intravenous antibiotics. Standard intensive care management regarding ventilation, circulation, sedation and fluid therapy was given according to current sepsis guidelines.[17] Mean arterial pressure, CPP, ICP and $PbtO_2$, was monitored

continuously and registered every hour when a microvial was analyzed. Treatment of elevated ICP was defined as a direct action done due to elevated ICP and with the aim of lowering the ICP. This treatment included CSF drainage, sedation with midazolam and fentanyl and/or infusion of hypertonic saline aiming at ICP <20 mmHg and a CPP> 60 mmHg.

Clinical outcome was evaluated utilizing Glasgow Outcome Score (GOS) at one month after discharge by a specialist in infectious diseases.

Intracerebral monitoring

ICP was monitored utilizing a pressure sensitive transducer (Camino® catheter, Integra Neurosciences Ltd. New Jersey, USA) positioned in the white matter of the right frontal lobe. The $PbtO_2$ and the microdialysis probes were via the triple lumen bolt positioned close to each other. $PbtO_2$ was measured with a Licox® probe (Licox CCISB, Integra Neurosciences Ltd. New Jersey, USA) placed 15 mm into the brain parenchyma. Data were collected using the AC3.1 monitor (Integra Neurosciences Ltd.) and recorded every 20 seconds. Microdialysis probes (70, MDialysis, Stockholm, Sweden) were perfused with artificial CSF (MDialysis, Stockholm, Sweden) at a rate of 0.3µl/min (106 MD pump, MDialysis, Stockholm, Sweden). The dialysates were collected in microvials and analyzed for glucose, lactate, pyruvate, glutamate and glycerol every 60 minutes using an Iscus Flex analyzer (MDialysis, Stockholm, Sweden). After insertion all probes were allowed a minimum of two hours for stabilization. The base-line levels for the various variables were established during the subsequent 60 minutes.

Microdialysis samples were obtained every hour for a maximum of 5 days due to the durability of the probes. In some cases it was not possible to start collecting microdialysis vials at the same time as the ICP monitoring started due to a delay with the clinical staff that worked on the project. ICP and $PbtO_2$ values described in the section 'physiological data' were collected concurrently with microdialysis vials. For all patients included with biochemical data, measurements were available for a minimum period of 48 hours.

Statistical analysis

For continuous variables, to evaluate the subjects' characteristics, a descriptive analysis was performed. Normality was tested graphical with quantile-quantile (Q-Q) plot. All measurements with normal distribution were presented as mean (± standard deviation). If there was skewed

distribution data were presented as median (25^{th}-75^{th} percentiles). To identify the differences in population means over time a one-way ANOVA was performed. A regression with robust variance estimator was used to identify differences in means between groups.

The correlation between variables was evaluated by calculating the Pearson correlation coefficient (r).

$P < 0.05$ was considered to be statistically significant. Data management were undertaken with a Microsoft Excel (Microsoft, Seattle, WA, USA) spreadsheet and analysed using Stata, version 14.2 (c).

Results

Basic clinical data

Ten patients were included in the study. Median age of the patients was 69 years (iqr 61-70) and median GCS during the initial 3h was 12 (iqr 7 – 14). After admission to hospital all patients deteriorated in GCS and were transferred to the intensive department. All were intubated and treated with controlled ventilation. Table 1 and 2 gives basic clinical information regarding the ten patients included in the study.

All cases had a verified microbiology diagnosis (Table 1). All patients had a blood culture drawn within the first 3 hours of admission and in eight cases they were positive. Microscopy of CSF was performed in all cases with gram-positive cocci seen in seven cases. Eight patients had bacterial growth in the CSF and one additional was positive with polymerase chain reaction for S. mitis.

Outcome assessed using GOS was median 3 (iqr 3-4) and in hospital mortality was 20%. No patient died during the 5 day period of multi-modal monitoring but two patients died within 1 month both during hospitalization. Patient 1 died on the day of planned discharge after completing antibiotics, rated stable and recovering to GCS 15. Cause of death was not clear. Patient 5 died during treatment in the intensive care department without regaining consciousness at any time during hospitalization. This patient had the longest delay from admission until correct diagnosis was given of all the patients. The delay until correct antibiotic treatment was given was 19.5 hours. An autopsy was not performed in any of the cases.

The ICP monitoring was stopped because of clinical improvement in all patients except for patient 5 who had active treatment withdrawn.

Physiological data

During the initial 3 hours of multi-modal monitoring mean ICP was 17 ± 15.4 mmHg and mean $PbtO_2$ was 17 ± 5.1 mmHg. The variations in mean ICP during the first 48 hours of treatment are shown in figure 1. The increase in mean ICP that occurred approximately 20-24 hours after initiation of monitoring was entirely due to a transitory marked increase in one patient (Pat. 3 in Table 1). In this patient LP ratio remained within normal limits during the entire study period and the observed increase in ICP was not associated with any change in $PbtO_2$ or LP ratio. Apart from the transient increase observed in this patient ICP remained close to normal in all patients during the study period. No significant difference in ICP means over the 48 hours was demonstrated (p=0.86).

During the monitoring period a gradual increase in $PbtO_2$ was obtained as shown in figure 2. During the period 24-48 hours after start of monitoring mean $PbtO_2$ was 23 ±7.4 mmHg. No significant difference in ICP means, over the 48 hours period, was demonstrated (p=0.86).

Biochemical data

In one patient (Pat. 2) the microdialysis catheter was malfunctioning. The biochemical analysis is accordingly based on data from 9 patients. During the first 3 hours of monitoring mean LP ratio was 35 ± 9.2. The variations during the initial 48 hours of monitoring are shown in figure 2. During the period 24-28 hours after start mean LP ratio was 29 ± 4.6. Figure 2 illustrates the simultaneous changes in mean $PbtO_2$ and LP-ratio. As shown in the figure the gradual increase in $PbtO_2$ occurred simultaneously with a decrease in mean LP ratio. No significant differences in LP-ratio or $PbtO_2$ means, over the 48 hours period, were demonstrated (p= 0.43 and p=0.92 respectively).

Normal reference levels of the biochemical variables were defined in accordance with data obtained from normal human brain utilizing identical microdialysis and analytical techniques.[18] According to these data the upper normal level of LP ratio was set at 30 (mean normal level + 2SD). Two patients in the present study exhibited normal LP ratios (*i.e.* below this upper limit) during the whole study period (Pats. 3 and 6). Data regarding LP ratio, $PbtO_2$, pyruvate, lactate, and glucose obtained in these patients during the initial 48 hours are given in Table 3. During this period simultaneous recordings of the variables were obtained during altogether 92 hours.

In six patients (Pats. 1,4,5,7-9) LP ratios above 30 were obtained simultaneously with normal or increased levels of pyruvate. In accordance with previous studies this metabolic perturbation was defined as mitochondrial dysfunction.[11,12] This biochemical pattern was obtained during altogether 143 hours. Table 3 gives the mean levels ± SD for the variables described above during the period defined as mitochondrial dysfunction. The table includes normal reference levels for the biochemical variables obtained in normal human brain.[18] Significant differences between the patient groups with normal biochemical variables or mitochondrial dysfunction were found in regards to LP-ratio ($p= 0.0006$) and glucose ($p= 0.03$).

In one patient (Pat. 10) a pattern indicating cerebral ischemia was observed during the period 2-10 hours after start of multi-modality monitoring (Fig. 3). In this patient a pronounced increase in LP ratio occurred simultaneously with marked decreases in the levels of pyruvate and glucoses as well as $PbtO_2$. During the episode shown in figure 3 median ICP was 9 mmHg. After the transient ischemic episode all biochemical variables returned to within normal limits[18] during the rest of the study period and the mean $PbtO_2$ was 18 ± 3.4 mmHg.

Figure 4 gives the correlation between $PbtO_2$ and LP ratio during the transient ischemic episode in pat. 10. For comparison the figure also shows the normal range of LP ratio (mean ± 2 SD). As illustrated in the figure there was a linear correlation between the two variables (Pearson $r = -0.9$). Figure 5 shows the correlation between $PbtO_2$ and LP ratio during the period of 143 hours of mitochondrial dysfunction shown in Table 3 including the normal range of LP ratio (mean ± 2 SD). In these patients there was no correlation between the two variables (Pearson $r = -0.05$).

Figure 6 shows the relation between $PbtO_2$ and LP ratio in the two patients defined as Normal LP ratio in Table 3. In these patients LP ratio remained below the upper normal limit of 30 during the whole study period. The figure illustrates that although LP ratio was within normal range the simultaneously measured PbtO2 varied between 8 and 32 mmHg (Pearson $r = 0.03$).

Discussion

Until now only two studies have been published describing cerebral energy metabolism in patients with severe community acquired meningitis.[8, 19] In both studies compromised cerebral energy metabolism was observed in 40-50% of the patients. Non-ischemic increase of LP ratio, presumably indicating mitochondrial dysfunction, was in both studies described by evaluating the pattern of the chemical variables obtained in a similar way as in other neurosurgical conditions.[11,12]

The differentiation between ischemia and mitochondrial dysfunction might improve by combining the biochemical analysis with simultaneous measurements of tissue oxygenation. From a theoretical perspective it would be anticipated that increased LP ratio at a simultaneous decrease in $PbtO_2$ is compatible with ischemia while an increase in LP ratio at an unchanged PbtO2 would indicate compromised oxidative metabolism of pyruvate – *i.e.* mitochondrial dysfunction. A recent experimental study of LPS-induced aseptic meningitis supported this interpretation.[10] In patients with meningitis experiences from monitoring PbtO2 have previously been published in only two case reports.[20,21] The present study is the first effort to compare and interpret these two variables during bacterial meningitis.

$PbtO_2$ varies with changes in arterial oxygen tension (PaO_2) and cerebral blood flow (CBF) but exactly what PbtO2 measures remains to be defined.[22] In an extensive clinical study Rosenthal et al. concluded that PbtO2 showed a strong relationship with local CBF.[23] Based on clinical observations several studies have suggested widely varying thresholds for $PbtO_2$ below which hypoxic/ischemic cerebral damage occurs.[24-26] In an experimental study it was verified that the threshold values for $PbtO_2$ under which energy metabolism fails was variable and most likely depending on the metabolic demands of the tissue.[27] Accordingly, in the present investigation we interpret the obtained level of $PbtO_2$ as a relative value of regional CBF which cannot by itself be used for definition of ischemia.

The LP ratio obtained during interstitial microdialysis is an accepted measure of cytoplasmatic red-ox state.[14, 28] An increase of LP ratio above the upper normal limit, defined according to Reinstrup et al.[18], indicates impaired cerebral oxidative metabolism which in turn may be caused either by insufficient oxygenation or mitochondrial dysfunction. Based on experimental and clinical studies utilizing microdialysis it has been suggested that in cerebral ischemia the obtained increase in LP ratio is associated with a decrease in pyruvate below normal lower limit while in mitochondrial dysfunction the increase in LP ratio occurs at a normal or increased concentration of pyruvate.[9-12,15] In the present study the data from simultaneous measurements of microdialysis (cytoplasmatic red-ox state) and $PbtO_2$ (local CBF) offers a possibility to support or falsify this hypothesis under clinical conditions.

In patient no. 10 (Fig. 3) a marked, transient increase in LP ratio occurred simultaneously with pronounced, transient decreases in local CBF ($PbtO_2$) and substrate (glucose). The simultaneously obtained decrease in pyruvate is in accordance with previous experimental studies of ischemia.[13, 14]

Figure 4 shows that in cerebral ischemia there is a linear correlation between LP ratio and $PbtO_2$ (Pearson correlation coefficient r = -0.9).

Patients exhibiting an increase in LP ratio simultaneous with a normal or increased level of pyruvate were in accordance with our hypothesis tentatively classified as mitochondrial dysfunction (Table 3). Figure 5 shows that in this group of patients there was no correlation between $PbtO_2$ and LP ratio (Pearson correlation coefficient r = -0.05). The observation documents that in these patients impaired oxidative energy metabolism was not caused by insufficient tissue oxygenation. The finding supports the hypothesis that a useful diagnostic separation between ischemia and mitochondrial dysfunction may be based exclusively on the biochemical pattern obtained during routine microdialysis.

In patients with a normal LP ratio (Table 3) $PbtO_2$ was very variable and obvious relation between $PbtO_2$ and LP ratio was obtained (Fig. 6). As shown in Table 3 there was no difference in mean $PbtO_2$ between patients with meningitis and a normal LP ratio and those with mitochondrial dysfunction. The relatively high levels of lactate in patients with normal LP ratio are probably explained by the fact that the patients suffered from bacterial meningitis.[29] An increase in lactate concentration does not indicate compromised cerebral energy metabolism as long as LP ratio remains within normal limits. It is well established that variations in cerebral metabolic rate result in parallel changes in lactate and pyruvate and accordingly no change in LP ratio.[28]

The mechanisms underlying non-ischemic mitochondrial dysfunction in severe bacterial infections are incompletely understood. Experimental studies have shown that pneumococcal meningitis induces mitochondrial chain complex I (the first enzyme complex in the respiratory chain) inhibition in the brain which may cause impaired energy metabolism.[30] In septic patients an association between mitochondrial dysfunction and ATP depletion has been reported to be related to organ failure and impaired clinical outcome.[31] However, opinions differ regarding the clinical importance of mitochondrial dysfunction in these conditions. In a recent review it was pointed out that mitochondrial function is highly variable in sepsis and that data from young, healthy animals have not supported the view that mitochondrial dysfunction is the general denominator for multiple organ failure.[32]

Limitations of the study

The present study included a limited number of patients. The clinical background and etiology also varied in the studied group of patients. Accordingly the biochemical patterns described should not be expected to be reflected in clinical outcome. An evaluation of the possible clinical effects of transient cerebral ischemia and mitochondrial dysfunction in patients with severe bacterial meningitis will require a large prospective study.

Conclusions

The present prospective study demonstrates that compromised cerebral energy metabolism is common in patients with severe community acquired bacterial meningitis. A biochemical pattern indicating mitochondrial dysfunction was observed more frequently than a pattern indicating cerebral ischemia. The combined data obtained from simultaneous measurements of $PbtO_2$ and cerebral LP ratio support the hypothesis that it is possible to separate cerebral ischemia from mitochondrial dysfunction based on the biochemical pattern obtained by microdialysis.

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Conflict of interest

None

Acknowledgments

Biological material was stored in OPEN, Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark: www.sdu.dk/ki/open

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Table 1. Demographics, clinical characteristics and intracranial pressure values/treatment.

Patient	Age years	Gender M/F	GCS[a] Initial 3h	Etiology	Clinical notes	First ICP[b] mmHg	Mean ICP[b] (±SD) mmHg	Mean CPP[c] (±SD) mmHg	ICP[b] intervention	GOS[d] day 30
1	70	F	8	S. pneumoniae	Petechiae, sinusitis, seizures	11	12.3 (±2.9)	73.6 (±8.8)	None	1
2	59	F	11	S. pneumoniae	Pansinuitis	32	6.8 (±6.0)	88.6 (±13.8)	Sedation[e]	4
3*	56	F	7	S. pneumoniae	Brain edema, sinusitis, seizures, septic shock	10	8.7 (±9.4)	78.5 (±13.9)	1. Sedation[e] 2. HNaCl[f] 3. Lumbar drain	3
4	70	M	4	S. mitis	Otitis	31	14.2 (±10.4)	64.4 (±10.3)	Sedation[e]	3
5	85	F	14	S. pneumoniae	Otitis, seizures, septic shock	11	5.7 (±3.2)	85.2 (±13.4)	None	1
6	60	M	14	Gr. C strep.	Seizures	28	12.1 (±5.1)	77.3 (±8.4)	Sedation[e] and HNaCl[f]	3
7	68	M	12	S. pneumoniae	Septic shock	29	7.6 (±3.7)	89.6 (±10.9)	Sedation[e] and EVD[g]	4
8	70	M	14	S. pneumoniae	Sinusitis, otitis, seizures	16	10.3 (±4.4)	77.9 (±11.9)	Sedation[e]	3
9	63	F	7	S. pneumoniae	Sinusitis, seizures, septic shock, dialysis	11	10.4 (±3.7)	93.4 (±14.2)	None	3
10	76	F	15	S. pneumoniae	Hydrocephalus, septic shock	7	4.9 (±5.3)	89.1 (±16.5)	None	4

[a] GCS: Glasgow Coma Scale, [b]ICP: Intracranial pressure, [c] CPP: Cerebral perfusion pressure, [d] GOS: Glasgow Outcome Scale, [e] Sedation: Treatment with midazolam and fentanyl. [f] HNaCl: Hypertonic saline, [g] EVD: External ventricular drain,

* Patient 3/ICP treatment: The numbering indicates that the interventions were not performed simultaneously but subsequently due to the lack of effect of the above intervention.

Table 2 Diagnostics, infection parameters, lumbar puncture and outcome.

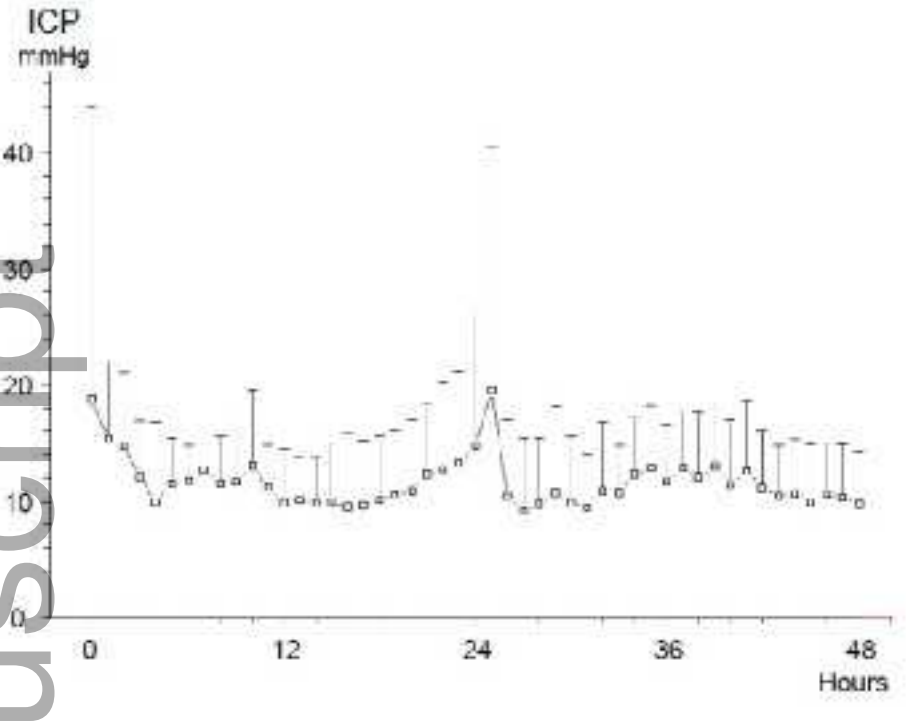
Diagnostics and treatment	**Time hours minutes, median (iqr[a])**
Time from admission to lumbar puncture	2h 57m (1h 52m – 8h 59m)
Time from admission to blood culture	16m (7m - 32m)
Time from admission to head CT scan	1h 15m (55m – 3h 14m)
Time from admission to antibiotics for meningitis	1h 58m (26m – 8h 59m)
Infection parameters	**Number, median (iqr)**
Temperature °c	39.3 (38.7 – 39.5)
CRP mg/l	98.5 (23.5 - 251.8)
Neutrophils mm^3	16.1 (11.1 - 26.4)
Lumbar puncture	**Number, median (iqr)**
CSF[b] - white blood cell count mm3	2369 (654 - 4065)
> Neutrophil cells mm^3	2132 (612 - 3910)
> Mononuclear cells mm^3	73 (30 - 281)
CSF – Red blood cells mm^3	299 (60 - 799)
CSF - Protein g/l	5.5 (3.8 - 8.2)
CSF - Lactat mmol/l	18.5 (15.5 - 19.3)
CSF - Glucose mmol/l	0.2 (0.2 - 2.2)
Intensive care department	**Time days – hours, median (iqr)**
Duration of stay ICU[c]	12d 18h (10d 21h – 13d 8h)
Duration ICP[d] monitoring	6d 6h (5d 15h -7d)
Outcome	**Number, median (iqr)**
Glasgow Outcome Score day 30	3 (3 - 4)

[a]iqr: interquartile range, [b]CSF: cerebrospinal fluid, [c]ICU: intensive care department, [d]ICP: intracranial pressure.

Table 3. Cerebral energy metabolism, intracranial pressure and cerebral perfusion pressure in 9 patients with severe bacterial meningitis.

	Normal (n=2) N=92 hours **Mean ± SD**	**Mitochondrial dysfunction (n=7)** N=143 hours **Mean ± SD**	**P**	**Normal reference[f] Mean ± SD**
LP[a] (ratio)	24 ± 4	36 ±5	0.0006	23 ± 4
$PbtO_2$[b] (mmHg)	18 ± 6	20 ± 6	NS[e]	
Pyruvate (µmol/L)	228 ± 94	132 ± 31	NS	166 ± 47
Lactate (mmol/L)	5.3 ± 1.9	4.5 ± 1.2	NS	2.9 ± 0.9
Glucose (mmol/L)	1.9 ± 0.6	0.9 ± 0.6	0.03	1.7 ± 0.9
ICP[c] (mmHg)	10.9 ±7	9.5 ± 5.4	NS	
CPP[d] (mmHg)	77.7 ± 10.6	82.6 ± 14.7	NS	

[a]LP: lactate/pyruvate ratio. [b]$PbtO_2$: brain tissue oxygen tension. [c]ICP: intracranial pressure. [d]CPP: cerebral perfusion pressure. [e]NS: not significant. [f]Data from Reinstrup et al [18].



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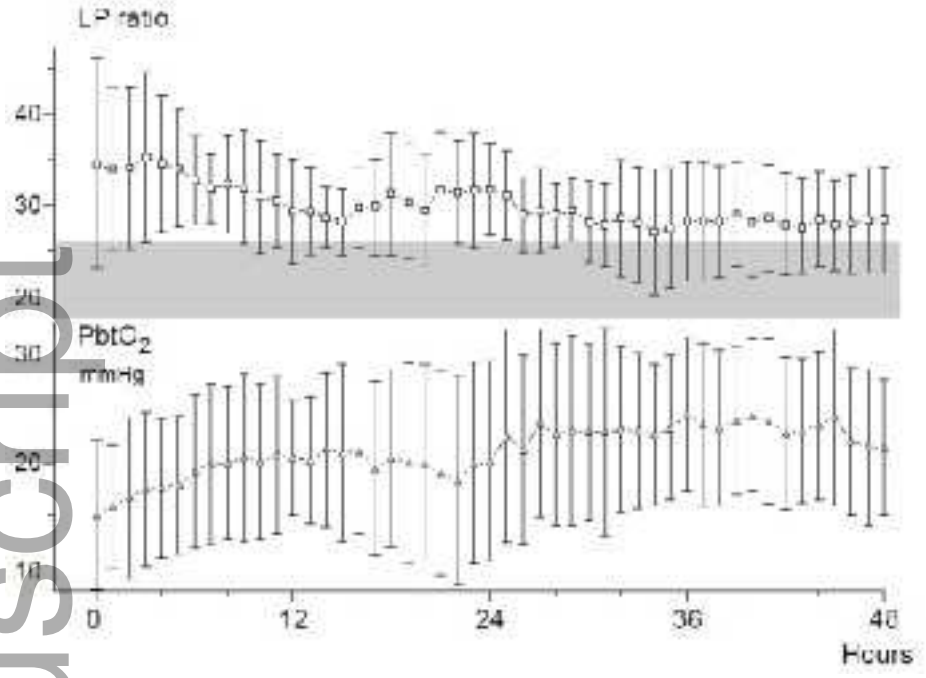

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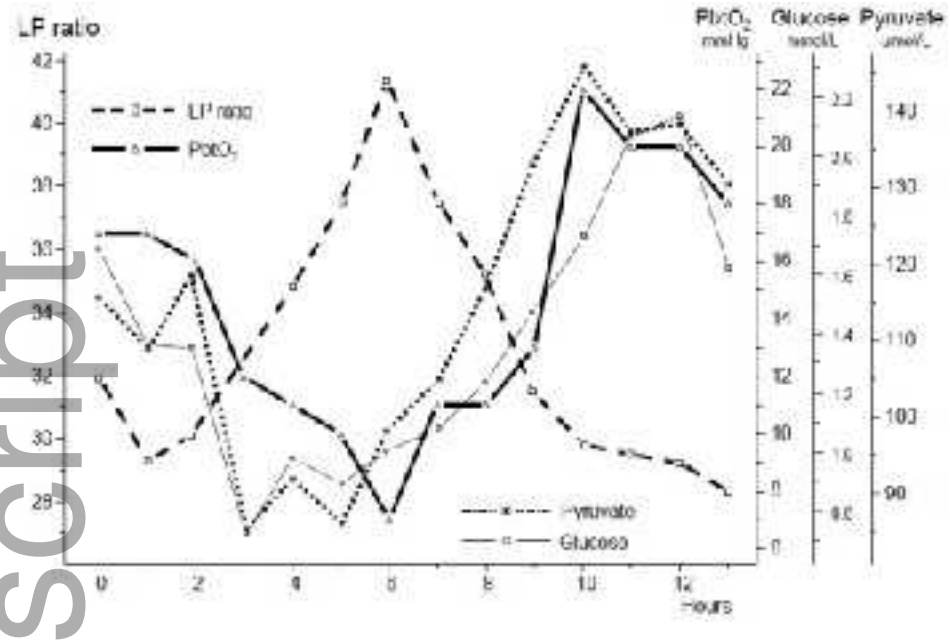

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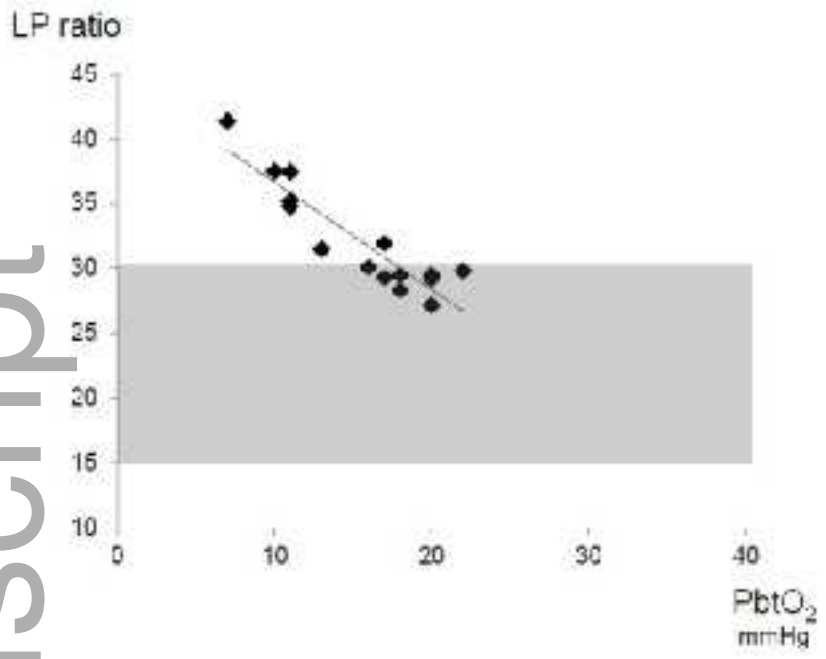

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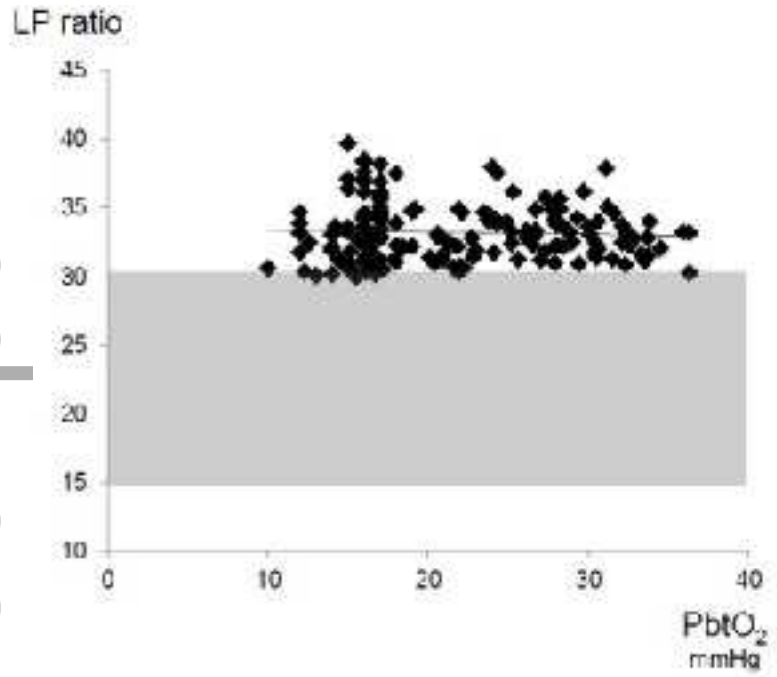

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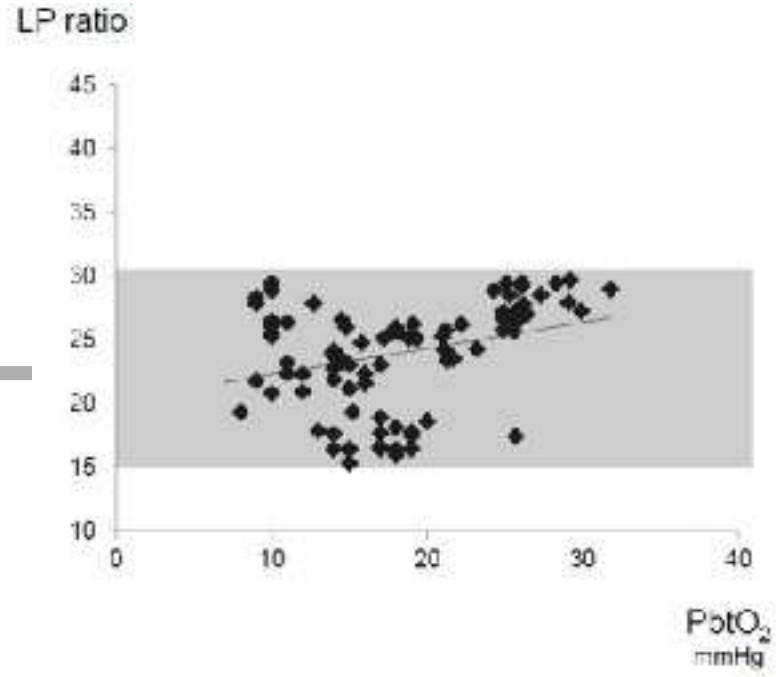

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