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The Role of Cerebrospinal Fluid Biomarkers in the Diagnosis of Post-Neurosurgical Meningitis

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ABSTRACT

AIM: To measure cytokine and lactate levels in the cerebrospinal fluid (CSF) of patients with suspected post-neurosurgical meningitis.

MATERIAL and METHODS: Interleukin (IL)-8,-12, and -13, interferon (IFN) gamma, and lactate concentrations were determined in the CSF of patients diagnosed with meningitis, who were undergoing follow-up after neurosurgical procedures at the Neurosurgery Clinic between May 2016 and November 2017. The demographic, clinical, biochemical, CSF cell count, CSF biochemistry, and CSF culture results of 119 patients were recorded.

RESULTS: The study group consisted of 39 patients diagnosed with post-neurosurgical meningitis. The control group comprised of 80 patients without pleocytosis, who had undergone lumbar puncture due to various indications. In the study group, 59% of the patients had fever, 66.7% had deterioration in the level of consciousness, and 35.9% had neck stiffness. The levels of IL-8 (96.5 ng/L vs. 86.6 ng/L, p<0.001), IL-12 (10.1 ng/L vs. 3 ng/L, p<0.001), and lactate (5.9 mmol/L vs. 2.1 mmol/L, p<0.001) were higher in the CSF of the patient group compared to the control group. However, IL-13 (32.7 ng/L vs. 42.5 ng/L, p=0.003) and IFN gamma (73.3 ng/L vs. 260.4 ng/L, p<0.001) levels were lower in patients compared to controls. The mortality rate in post-neurosurgical meningitis patients was estimated to be 35.9%.

CONCLUSION: Post-neurosurgical meningitis prolongs the duration of hospital stay and causes long-term sequelae. Therefore, measurement of CSF cytokine and lactate levels alongside meningitis diagnostic processes may facilitate early and accurate diagnosis. Measuring CSF lactate is inexpensive and cost effective, particularly in post-neurosurgical patients.

KEYWORDS: Cerebrospinal fluid, Cytokines, Lactate, Meningitis, Neurosurgery, Post-neurosurgical meningitis

ABBREVIATIONS: CSF: Cerebrospinal fluid, **NCM:** Nosocomial meningitis, **IL-8:** Interleukin-8, **IL-12:** Interleukin-12, **IL-13:** Interleukin-13, **IFN- γ:** Interferon gamma, **LP:** Lumbar puncture, **CDC:** Centers for disease control, **ELISA:** Enzyme-linked immunosorbent assay, **GCS:** Glasgow coma scale, **CRP:** C-reactive protein, **ICU:** Intensive care unit, **MIF:** Meningeal irritation findings, **WBC:** White blood cell, **HGB:** Hemoglobin, **HTC:** Hematocrit, **AST:** Aspartate aminotransferase, **ALT:** Alanine aminotransferase, **PCT:** Procalcitonin, **SBGL:** Simultaneous blood glucose level, **TNF-α:** Tumor necrosis factor alpha, **IL-1:** Interleukin-1, **BM:** Bacterial meningitis

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INTRODUCTION

The incidence of bacterial meningitis after neurosurgical interventions varies between 0.3% and 1.5%. Although the incidence is low, high morbidity and mortality rates following the development of meningitis are significant clinical problems (3,11). Blood, bone powder and surgical implants may lead to aseptic meningitis in the postoperative period. Cell counts and biochemical parameters (such as protein and glucose levels) measured in cerebrospinal fluid (CSF) have limited capability in differentiating nosocomial meningitis (NCM) from postoperative aseptic meningitis (21). CSF culture is the gold standard for the diagnosis of NCM. However, time required for bacterial growth and antibiotic susceptibility in culture results in delayed diagnosis. Therefore, in recent years, the usefulness of serum and CSF cytokine and lactate concentrations in the differential diagnosis of bacterial versus viral meningitis rapidly gaining prominence. Besides being cheap and readily available, tests quantifying lactate concentrations in CSF have the added benefit of being unaffected by leukocytes and erythrocytes in the CSF (5,10).

In this study, we aimed to measure the levels of interleukin-8 (IL-8), interleukin-12 (IL-12), interleukin-13 (IL-13), interferon-γ (IFN-γ), and lactate in CSF samples obtained from patients with suspected NCM. Furthermore, we sought to investigate the role of these tests in early diagnosis of meningitis and its relationship to patient prognosis.

MATERIAL and METHODS

The CSF samples were obtained from patients who had been diagnosed with meningitis and followed-up in the Infectious Diseases and Neurosurgery Clinics, and Intensive Care Unit between May 2016 and November 2017. After collection, the samples were placed in Eppendorf tubes and stored in the freezer at –80 ºC.

A total of 119 patients aged 18 years and above were included in the study. Results of CSF direct examination, CSF biochemical tests (glucose, concomitant blood sugar, and protein concentration), culture results, complete blood count, serum biochemistry, and other clinical findings of the patients were prospectively recorded. CSF samples were obtained from patients who had undergone neurosurgical intervention and were diagnosed with NCM without pleocytosis, displaying the clinical signs and symptoms of meningitis (Group 1). Patients who had undergone lumbar puncture due to indications other than NCM were included in the control group (Group 2). The CSF samples were collected from 39 patients in group 1 and from 80 patients in Group 2.

Nosocomial central nervous system infections were determined based on criteria outlined by the Centers for Disease Control (6). On the day of the tests, the collected CSF samples were thawed at room temperature. The cytokines (IL-8, IL-12, IL-13, and IFN-γ) and lactate levels were measured with Sunred biobranded kits (Shanghai Sunred Biological Technology Co., Ltd; Shangai, China), by using microelisa method. In addition, the age, gender, and Glasgow Coma Score of patients were evaluated along with blood leukocyte and platelet counts, serum C-reactive protein levels, and treatment durations.

The study was approved by the Medical Research Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital with the decision number 44/9 on December 25, 2017.

Statistical Analysis

Descriptive and advanced analyses were performed using the SPSS, Open Epi and Excel programs. Some of the graphs were prepared using the Excel program and some of them were prepared using the SPSS program.

While evaluating the data, the numerical and percentage distributions, 95% confidence interval (GA), 5% error margin ($p<0.05$), and estimated relative risk (OR) calculations were used to identify the possible risk factors. Both the mean and the median values are presented to make the distribution of data easy to understand.

The Chi-square test, Fisher's exact test and the mid-P exact test were used for evaluation of the categorical variables. To evaluate the difference between the means, significance tests for the difference between the means was used (independent Student's t-test in normally distributed data and Mann-Whitney U test in non-normally distributed data).

ROC curves were drawn and the area under the curve (AUC) was calculated to determine whether or not cytokine levels could be an indicator in the diagnosis of meningitis in the NCM and control groups. Accordingly, the optimum cut-off points for each cytokine were determined based on the highest AUC value.

Relative risk calculations with 95% confidence interval (GA) and 5% error allowance ($p<0.05$) were used to evaluate the factors affecting death and survival.

RESULTS

Of the 39 NCM patients, 17 were female (43.6%), 22 were male (56.4%), and the mean age was 51.6 years. The control group comprised 40 women and 40 men.

The clinical features and the physical examination findings of the study groups are presented in Table I.

There was a statistically significant difference between the NCM group and control group with regard to fever and altered mental status ($p<0.005$). There was also a significant difference between the study groups in the presence of meningeal inflammation signs such as nuchal rigidity and Kernig–Brudzinski sign ($p<0.005$).

We found a statistically significant difference in the white blood cell count, percentage of neutrophils, and serum CRP levels at the time of diagnosis in patients with NCM compared to the control group ($p<0.05$). In the CSF, leukocyte counts, glucose and protein levels were significantly higher in the NCM group than the controls ($p<0.05$). IL-8 IL-12, and lactate levels were higher in CSF of NCM patients compared to the control group, whereas IL-13 and IFN-γ levels were significantly lower ($p<0.05$).

In addition, the CSF culture of the NCM group resulted in bacterial growth in 16 of 39 patients. Seven of the bacteria in the CSF culture were gram-positive and nine were gram-negative. In the species analysis of these culture-grown bacteria, six were found to be *Acinetobacter baumanii,* five were *coagulase-negative staphylococci,* one was *Serratia marcescens*, one was *Enterococcus spp*, one was *Escherichia coli,* one was *Pseudomonas aeruginosa*, and one was *methicillin-resistant Staphylococcus aureus.*

The hematological findings, CSF analysis results and CSF cytokine levels of the participants are presented in Tables II-IV.

The mortality rate in NCM patients was calculated as 35.9%. The ROC analysis results are displayed in Table V, Figures 1 and 2.

DISCUSSION

The diagnosis and treatment of post-neurosurgical bacterial meningitis is challenging. Currently, the diagnosis of NCM is based on detection of the bacterial strain and Gram staining in CSF cultures. Since some patients may have previously used antibiotics, culture negativity may not be sufficient to rule out meningitis (16). Uncertainty and difficulty in diagnosis can lead to increased mortality and cost (4,13,16). Therefore, it is necessary to conduct relevant clinical trials to develop early diagnostic biomarkers for meningitis (23).

Elevated CSF cytokine levels are undisputed markers of meningeal inflammation; however, there is no consensus on the threshold values of cytokine concentration for the differential diagnosis of bacterial versus viral meningitis. Tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and IL-8 are among the first cytokines released after infection (13,18). Although CSF lactate levels can differentiate between bacterial and viral meningitis in the pediatric population, its use in the adult population is limited (2,7).

Table I: Clinical Features and Physical Examination Findings of the Patients in the Nosocomial Meningitis and the Control Groups

Clinical Features	**NCM group (n=39)**		**NCM/C**		**Control group (n=80)**	
	n	**%**	**OR (%95 CI)**	**p**	**n**	**%**
Fever	23	59.0	**2.8 (1.3-6.2)**	**0.009**	27	33.8
Seizure	5	12.8	0.8 (0.3-2.6)	0.750	12	15.0
Consciousness State						
Unconscious/Confused	26	66.7	**2.7 (1.2-6.0)**	**<0.013**	34	42.5
Conscious	13	33.3			46	57.5
Headache	10	25.6	0.6 (0.3-1.4)	0.247	29	36.3
Nausea-vomiting	14	35.9	1.0 (0.5-2.3)	0.923	28	35.0
Nuchal rigidity	14	35.9	**3.5 (1.4-8.8)**	**0.005**	11	13.8
Focal neurological finding	1	2.6	0.7 (0.1-6.7)	1.000*	3	3.8
Antibiotic use	19	48.7	**9.9 (3.7-26.9)**	**<0.001**	7	8.8
ICU requirement	28	71.8	**48.4 (14.2-164.4)**	**<0.001**	4	5.0
MIF present	2	5.1	-	0.106*	-	-
GCS						
≤13 points	24	61.5	**6.4 (2.8-14.9)**	**<0.001**	16	20.0
>13 points	15	38.5			64	80.0
Physical Examination Findings	**Mean ± SD**	**Median (Min-Max)**			**Mean ± SD**	**Median (Min-Max)**
Body Temperature (ºC)	37.9 ± 1.0	38.2 (36.2-40.0)	-	**0.002**	37.3 ± 1.0	36.8 (36-40)
GCS	10.9 ± 4.3	13.0 (2.0-15.0)	-	**<0.001**	14.1 ± 1.7	15 (4-15)
Pulse (beat/min)	82.3 ± 17.2	80 (54-122)	-	0.117	77.6 ± 14.4	78 (50-120)
Respiration count (resp/min)	20.1 ± 1.8	20 (18-26)	-	**0.006**	19.1 ± 1.7	18 (14-24)

Fischer's Exact Chi-square test* ***NCM:* *Nosocomial meningitis,* ***C:*** *Control,* ***ICU:*** *Intensive care unit,* ***MIF:*** *Meningeal irritation findings (Kernig-Brudzinski sign),* ***GCS:*** *Glasgow coma score.*

In our study, meningitis patients were found to have meningitis of nosocomial origin at a rate of 12.8% when evaluated on the basis of three classical symptoms: fever, neck stiffness, and altered consciousness levels. The rate of NCM was determined to be 66% by Hussein and Shafran, 44% by van de Beek et al., and 59% by Weisfelt et al. (9,20,22). Our rate may be lower than that reported in the literature due to the low number of cases, the older age of patients and the inaccurate evaluation of neck stiffness. Evaluating patients based on the three classical symptoms may lead to some cases being overlooked, making it a possible limitation of our study.

Table II: Hematological Findings of the Nosocomial Meningitis and the Control Groups

Hematological Findings	NCM group (n=39)		NCM/C	Control group (n=80)	
	Mean ± SD	Median (Min-Max)	p	Mean ± SD	Median (Min-Max)
WBC (10^3/µl)	14.3 ± 12	10.5 (1.2-60.9)	**0.050**	10.3 ± 4.9	9.2 (2.7-29.1)
Neutrophil (%)	78.8 ± 10.0	80.0 (52.0-95.0)	**<0.001**	69.0 ± 12.7	70.0 (36.0-90.0)
CRP (mg/L)	98.8 ± 81.2	79.0 (7.7-276.0)	**0.002**	44.7 ± 67.8	17.5 (1.6-262.0)
Hg (g/dl)	11.5 ± 2.2	11.5 (8.2-16.7)	**<0.001**	13.1 ± 1.9	13.1 (7.8-17.8)
Htc (%)	34.2 ± 6.	33.6 (24.4-51.4)	**<0.001**	38.7 ± 5.7	39.2 (22.5-53.8)
Platelets (10^3/µl)	287 ± 168	230 (109-985)	0.067	233 ± 82.5	226 (22-431)
Urea (mg/dl)	41.2 ± 29.4	31.0 (12.0-143.0)	0.289	48.9 ± 40.8	36.5 (0.6-238.0)
Creatinine (mg/dl)	1.0 ± 0.7	0.8 (0.5-4.2)	0.289	1.5 ± 3.1	0.9 (0.4-28.0)
AST(U/L)	121.3 ± 477.3	26.0 (9.0-3010.0)	0.274	35.9 ± 78.8	23.0 (8.0-714.0)
ALT(U/L)	109.2 ± 371.3	32.0 (7.0-2347.0)	0.167	25.4 ± 23.2	19.0 (4.0-129.0)
ESR (mm/hr)	34.3 ± 23.9	28.0 (4.0-100.0)	0.104	25.1 ± 22.2	21.5 (2.0-120.0)
PCT (ng/ml)*	31.8 ± 46.6	12.9 (1.6-100.0)	0.256	8.9 ± 16.4	0.2 (0.1-43.0)

***PCT (procalcitonin) was measured in 4 patients with nosocomial meningitis and in 7 control subjects. **NCM:** Nosocomial meningitis, **C:** Control*
Fischer's exact chi-square test.

Table III: CSF Findings of the Nosocomial Meningitis and the Control Groups

CSF Findings	NCM group (n=39)		NCM/C	Control group (n=80)	
	Mean ± SD	Median (Min-Max)	p*	Mean ± SD	Median (Min-Max)
Leukocyte count (/mm^3)	754.6 ± 1444.4	367.5 (20-8400)	**<0.001**	8.2 ± 22.1	0.0 (0.0-150.0)
Erythrocyte (/mm^3)	44018.3 ± 106461.3	1690 (0-409600)	**<0.001**	1053.1 ± 7420.3	0 (0-65760)
Glucose (mg/dl)	53.9 ± 29.1	56 (2-120)	**<0.001**	86.4 ± 47.2	71.0 (30.0-355.0)
Protein (mg/dl)	483.2 ± 1284.6	154 (31-7825)	**<0.001**	54.5 ± 31.3	47.0 (15.0-206.0)
CSF glucose / SBGL	0.39 ± 0.17	0.43 (0.02-0.70)	**<0.001**	0.64 ± 0.21	0.60 (0.32-1.45)
Protein value (mg/dl)	**n (%)**	**OR (%95 CI)**	**p**	**n (%)**	**-**
High (≥45)	35 (94.6)	**15.1 (3.4-66.9)**	**<0.001**	43 (53.8)	-
Normal					

NCM:** Nosocomial meningitis, **C:** Control, **CI:** Confidence interval, **SBGL:** Simultaneous blood glucose level. **Mann-Whitney U test.

Table IV: CSF Interleukin and Lactate Levels of the Nosocomial Meningitis and the Control Groups

	NCM group (n=39)		NCM/C	Control group (n=80)	
	Mean ± SD	**Median (Min - Max)**	**p***	**Mean ± SD**	**Median (Min - Max)**
Interleukin-8 (ng/L)	96.5 ± 22.9	97.0 (26.5 - 171.1)	**<0.001**	86.6 ± 18.8	86.2 (48.4-179.2)
Interleukin-12 (ng/L)	10.1 ± 3.9	10.4 (2.9 - 20.0)	**<0.001**	3.0 ± 0.7	3.0 (0.1-4.5)
Interleukin-13 (ng/L)	32.7 ± 17.9	29.5 (0.0 - 78.6)	**0.003**	42.5 ± 18.0	35.1 (20.1-128.0)
Interferon-γ (ng/L)	73.3 ± 46.4	58.0 (0.4 - 197.7)	**<0.001**	260.4 ± 30.2	264.7 (195.1-339.3)
Lactate (mmol/L)	5.9 ± 4.7	4.8 (0.2 - 22.9)	**<0.001**	2.2 ± 1.1	2.0 (0.2-6.1)

NCM: *Nosocomial meningitis,* ***C:*** *Control.* *******Mann-Whitney U test.*

Table V: ROC Curve Analysis Results of Patients with Nosocomial Meningitis according to Variables

	Cut-off point	**Sensitivity (%)**	**Specificity (%)**	**AUR OC* (95% CI)**	**p**
NCM/Control					
IL-8	≥85.8	67.6	46.8	68.2 (56.7-79.7)	**0.002**
IL-12	≥3.2	94.6	64.6	96.9 (93.1-100.0)	**<0.001**
IL-13	≤42.3	67.6	40.0	67.0 (55.0-79.0)	**0.003**
IFN-γ	≤200	100.0	99.9	99.9 (99.7-100.0)	**<0.001**
Lactate	≥2.4	83.8	70.9	85.4 (76.3-94.4)	**<0.001**
CSF Leukocyte count	≥12.5	100.0	98.6	98.8 (97.6-100.0)	**<0.001**
CSF Protein level	≥70	89.2	99.8	91.7 (85.7-97.7)	**<0.001**
CSF Glucose/SBGL	≤0.54	78.4	63.7	82.0 (74.3-89.8)	**<0.001**

NCM: *Nosocomial meningitis,* ***C:*** *Control.*

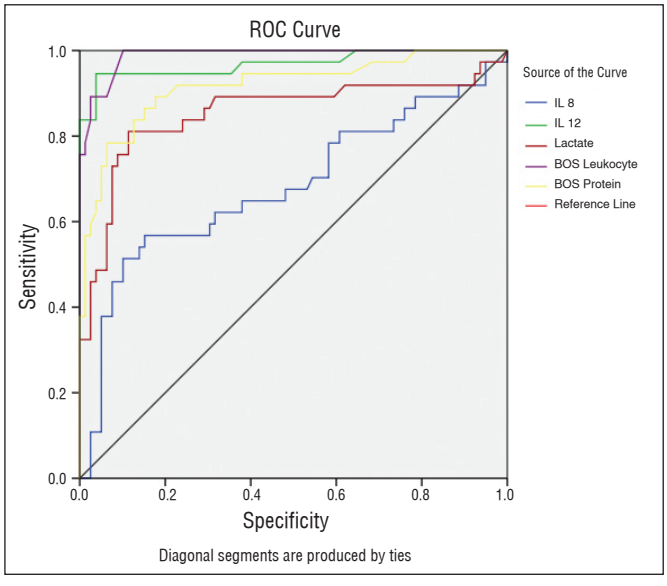

Figure 1: ROC curve analysis of CSF leukocyte count, CSF protein, IL-8, IL-12 and lactate levels presented.

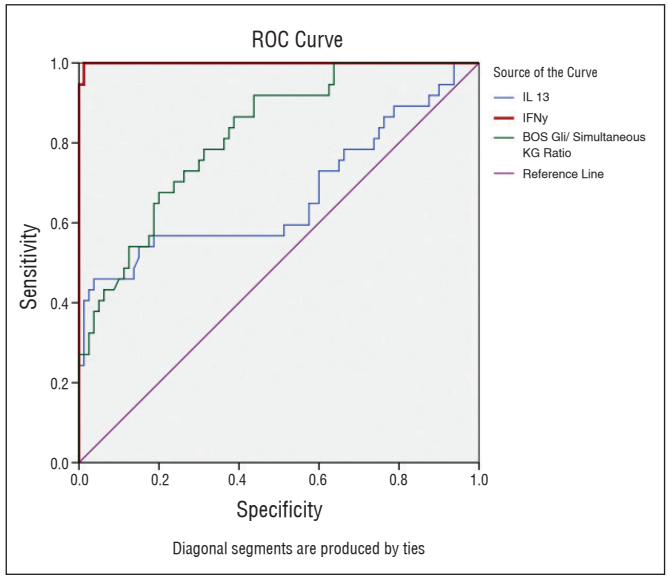

Figure 2: ROC curve analysis of CSF glucose/SBGL, CSF IL-13 and IFN-γ levels presented.

The mean IL-8 level in our NCM patient group was 99.5 ng/L and the mean level in the control group was 86.6 ng/L. Most studies in the literature are focused on the differential diagnosis of bacterial-viral meningitis instead of developing a definitive diagnosis. Lopez-Cortes et al. observed a significant difference in IL-8 levels between the pyogenic meningitis group and the control group (12). Such studies mainly include patients with community-acquired meningitis. Although our comparison is limited due to the low number of studies associated with nosocomial meningitis, elevated IL-8 levels in CSF can be used to distinguish aseptic meningitis, especially in patients with nosocomial meningitis.

In our study, the mean IL-12 level was 10.1 ng/L and 3 ng/L in patients with NCM and the control group, respectively. There was a statistically significant difference between these two groups. In their study on patients with bacterial meningitis, Perdomo-Celis et al. showed that high IL-12 levels were associated with poor prognosis (15). Therefore, high IL-12 levels in our patient group may be an early indicator of bacterial meningitis and differential diagnosis of aseptic meningitis.

The mean IFN-γ concentration in our study's NCM group was 73.3 ng/L and in the control group was 260.4 ng/L. In contrast, the study by Ohga et al. showed that the mean IFN-γ level in aseptic meningitis patients was higher than the bacterial meningitis and the control groups (14). The heterogeneity in our control group may have led to this discrepancy. The presence of patients with neurological disorders within this group may result in higher IFN-γ levels in the control group. In addition, the time of CSF collection, being at different stages of infection and the small sample size of the control group are some of the other limitations.

In our study, the mean IL-13 levels were 32.7 ng/L and 42.5 ng/L in the NCM patient group and in the control group, respectively. Consistent with our data, Belogurov et al. also found lower CSF IL-13 levels in meningitis patients than the control group (1). Therefore, our findings may help overcome the problem of insufficient number of studies in the literature.

In accordance with the two published meta-analyses, CSF lactate level has been shown to be a better marker than most conventional CSF markers in differentiating community-acquired bacterial meningitis from aseptic meningitis (10,17). The mean CSF lactate level in the NCM patient group was 5.9 mmol/L, and in the control group was 2.2 mmol/L, in our study. In the study by Grille et al., the mean CSF lactate level in patients diagnosed with postoperative meningitis was found to be 10.72 mM, the mean CSF lactate level in patients suspected of having postoperative meningitis was found to be 6.07 mM, and the mean CSF lactate level in patients without meningitis was determined to be 3.06 mM. There was no statistically significant difference between the lactate levels in patients with proven and probable meningitis, but there was a statistically significant difference between these groups and the patients without meningitis (8). Furthermore, Tavares et al. reported that the CSF lactate level was not affected by the number of red blood cells in CSF, thus supporting the accurate timing of diagnosis of meningitis in the postoperative period in NCM patients (19).

In addition, when we performed sub-group analysis in our NCM patient group, the mean lactate concentration in those who demonstrated growth in the CSF culture was 7.62 mmol/L and the mean lactate concentration of those with no growth was 5.03 mmol/L. Although no statistically significant difference was found between these values, they were higher than that of the control group. We think that the lack of statistical significance between the groups with and without growth in the CSF culture may be due to the low number of cases in our study.

CONCLUSION

Cytokine and lactate concentrations in CSF are important for early and accurate diagnosis in order to prevent the prolonged hospital stay, increased cost and long-term sequelae of NCM. Measuring the lactate levels in the CSF is a particularly cheap, easily accessible and repeatable test. However, more prospective studies in this area are required to determine the critical biomarker values and to obtain benefit from routine clinical use.

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