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Prospective observational cohort study of cerebrovascular CO_2 reactivity in patients with inflammatory CNS diseases

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ABSTRACT

PURPOSE

The purpose of this study was to evaluate the significance of cerebrovascular CO_2 reactivity (CO_2 R) in the course and outcome of inflammatory CNS diseases.

METHODS

Sixty eight patients with inflammatory CNS diseases and thirty healthy volunteers were included in this prospective observational cohort study. The observational period was between January 2005 and May 2009.

CO_2 reactivity was measured by Transcranial Doppler ultrasound (TCD) using the breath-holding method. We compared patients with normal CO_2 R ($BHI_m \geq 1.18$ = BHI_N group) with patients who showed impaired CO_2 R ($BHI_m < 1.18$ = BHI_R group). We also analyzed the association of impaired CO_2 R with the etiology, severity and outcome of disease.

RESULTS

When compared to BHI_N group, the patients from BHI_R group were older, had a heavier consciousness disturbance, experienced more frequent respiratory failure, and subsequently had worse outcomes. There were no fatalities among the 28 patients in the BHI_N group. The comparison of subjects with bacterial and non-bacterial meningitis revealed no significant differences. The unfavorable outcome of disease (GOS 1-3) was significantly more common in subjects with impaired CO_2 reactivity (62.5% vs. 10.7%).

Logistic regression analysis was performed in order to establish the prognostic value of BHI_m. The outcome variable was unfavorable outcome (GOS 1-3), while the independent variables were age, GCS and BHI_m. The age and BHI_m showed the strongest influence on disease outcome. A decrease of BHI_m for each 0,1 unit increased the risk of unfavorable outcome for 17%.

CONCLUSIONS

Our study emphasizes the importance of CO_2 reactivity assessment in patients with inflammatory CNS diseases.

Key words: CNS infections; bacterial meningitis; CO_2 reactivity; Transcranial Doppler (TCD); breath-holding

INTRODUCTION

Despite advances in the treatment of bacterial meningitis (BM), the overall mortality as well as long-term neurological sequelae are still high. This is particularly true with pneumococcal meningitis [1-4]. The most common factors associated with poor outcome in bacterial meningitis are seizures, advanced age, disturbed consciousness, the presence of multiple organ dysfunction, hypotension, APACHE II score > 13, pneumococcal etiology and delay in antimicrobial treatment [3-8].

Cerebrovascular dysregulation represents one of the most deleterious consequences of neuroinflammation [9]. The relevance of impaired cerebral blood flow (CBF) chemoregulation relies on subsequent hypoperfusion or global "luxury" perfusion.

In addition, although not caused by CO_2 reactivity (CO_2 R) loss, the severe blood-brain barrier disruption frequently occurs in these patients. Therefore, the aggravation of brain edema with the use of mannitol infusion due to heavy capillary leak can be expected in such patients.

Beside osmotic diuretics and steroids, the usual treatments for increased intracranial pressure include thiopental infusion and hyperventilation [10]. The latter often has limited effectiveness if cerebrovascular CO_2 reactivity is impaired.

The alternative and CO_2 reactivity-independent symptomatic treatments such as therapeutic hypothermia (TH) in such patients hold promise. The effects of mild therapeutic hypothermia may target the pathophysiological mechanisms in bacterial meningitis because the majority of them are temperature-dependent [11,12]. Even with this knowledge, the CO_2 reactivity (CO_2 R) has only been studied in very few patients with BM [13,14].

Transcranial Doppler ultrasound (TCD) is accepted and considered to be an appropriate technique for noninvasive assessment of cerebral arterioles reactivity because the changes in mean blood flow velocities (MBFV) correlate with the changes in CBF [15,16].

The aim of this study was to assess the cerebrovascular CO_2 reactivity measured by TCD using the breath-holding method in patients with inflammatory CNS diseases.

MATERIALS AND METHODS

The study was approved by the hospital ethics committee and informed consent was obtained from all examinees or their next of kin.

Data collection

This prospective study was performed between January 2005 and May 2009 at the University Hospital for Infectious Diseases in Zagreb. The following parameters were recorded in a database: age, gender, physical and neurological signs, mechanical ventilation (MV), cerebrospinal fluid (CSF) characteristics, microbiological findings in CSF and blood, mean arterial pressure (MAP), Glasgow Coma Scale score (GCS), Glasgow Outcome Scale score (GOS) and mean breath-holding index (BHI_m). Data was collected during the first 24 hours after admission to the Department and within the first five days of illness in all patients.

Patient selection

The patients were eligible for the study if they were 18 years of age or older and had inflammatory CNS disease. Patients were excluded if they had brain abscess, subdural empyema, nosocomial and shunt meningitis, spinal meningitis or myelitis, stroke, transitory ischemic attacks, carotid artery disease, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), diabetic microangiopathy, septic shock, death not related to meningitis, temporal bone "acoustic window" absence, or had been treated with sodium nitroprusside.

During the same time period thirty healthy volunteers were studied following written informed consent. All volunteers were examined and found to be healthy and without infection. The purpose of the control group was to establish the lowest value of the mean breath holding index (BHI_m) in healthy volunteers.

Definitions

Bacterial meningitis (BM) was diagnosed on the basis of clinical picture (fever, headache, neck stiffness and consciousness disturbance with or without seizures and neurologic deficits), supportive cerebrospinal fluid findings (pleocytosis, increased protein concentration and decreased CSF-blood glucose ratio) and a positive CSF culture; a negative CSF culture with a positive CSF PCR assay, a positive blood culture, or a positive Gram stain of a CSF sample.

Non-bacterial inflammatory CNS disease (NBM) was diagnosed on the basis of present encephalopathy with at least one of the following: fever, seizures, focal neurological findings; pleocytosis with increased protein concentration in the CSF; and a positive CSF or

blood culture (fungal meningitis); virus detection by PCR assay in CSF samples; proved intrathecal antibody production and electroencephalographic or neuroimaging findings consistent with encephalitis or acute disseminated encephalomyelitis (ADEM).

The patients` mental status was assessed using the Glasgow Coma Scale score (GCS). Recorded scores were the lowest during the first 24 hours after admission to the hospital. Altered mental status was defined as GCS < 15. The patients' clinical outcome was assessed by using the Glasgow Outcome Scale score (GOS) at the time of discharge from the hospital.

Unfavorable clinical outcomes included death (GOS 1), vegetative state (GOS 2) and severe neurological deficit (GOS 3). GOS 5 (mild or no disability) but also GOS 4 (moderate disability), were considered favorable outcomes because of extremely detrimental nature of CNS infections.

According to disease etiology, patients were divided into bacterial (BM) and non-bacterial (NBM) groups. Thirty healthy volunteers represented the control group.

Patients were stratified according to CO_2 reactivity into "BHI_N" (normal CO_2 reactivity defined with $BHI_m \geq 1{,}18$) and "BHI_R" (impaired CO_2 R defined with $BHI_m < 1{,}18$ according to BHI values in healthy volunteers) groups.

Measurements

TCD measurements of CO_2 reactivity were performed during the first 24 hours after admission to the hospital by using a Multidop 4 X (DWL, Sipplingen, Germany) with two 2-MHz pulsed wave probes 1.7 cm in diameter. The software used was TCD-8 for MDX (Version 8.0, Aaslid Rune). Normal basic hemodynamic parameters (mean arterial pressure and heart rate) and $PaCO_2$ [35-45 torr (4,67-6,0 kPa)] were confirmed in all examinees before measurements. Direct blood pressure monitoring was performed by cannilation of the radial artery. Thus we were able to note every change in the arterial pressure which potentially could interfere with the measurements.

The left and right middle cerebral arteries (MCA) were insonated simultaneously through the temporal bone windows at a depth of 50-55 mm. The probes were secured to the head of the patient with a specially designed spectacle frame that permitted a constant angle of insonation. The mean blood flow velocities (MBFV) were continuously recorded during normal ventilation and during breath holding.The CO_2 reactivity (CO_2 R) was assessed using the breath-holding method.

Spontaneously breathing and compliant examinees were asked to hold their breath after normal inspiratory breath for 30 seconds or less if it becomes uncomfortable.

Mechanically ventilated patients were sedated and relaxed before the procedure using midazolam and vecuronium bromide, respectively. The administered drugs have no significant effect on cerebral vasoreactivity and hemodynamics [17,18]. In that case the patients were

disconnected from the ventilator for 30 seconds. Assisted controlled ventilation (ACV) mode was used in all mechanically ventilated patients.

MBFV at the start and at the end of the breath hold period was recorded. The procedure was repeated after a five minute rest period and the mean values from both MCAs were taken for calculation. The breath-holding index (BHI) was calculated by dividing the percentage of MBFV increase during breath holding by the time (in seconds) of apnea. The mean breath-holding index (BHI_m) was calculated from both MCA (left and right MCA) breath holding indexes.

Statistical analysis

Univariate statistics included calculation of the mean value, standard deviation, median and interquartiles for continuous variables. Values for categorical variables were presented as frequencies.

Bivariate statistics assessed the differences between compared groups. The Mann-Whitney's test was used to estimate the difference amongst continuous variables. For categorical data the chi-square test and the Fisher's two-tailed exact test, were used when appropriate. All relevant demographic and clinical variables of the patient groups were compared.

The outcome variable was the Glasgow Outcome Scale Score (GOS). The correlation between BHI_m and the severity of disease was assessed using multivariate tests after bivariate analysis. Logistic regression analysis was performed to ascertain the independent predictive potential of CO_2 reactivity, after adjustment for potential confounding variables. The criteria for inclusion of variables in the logistics regression models were based on the evidence of an association in the bivariate analysis. P values less than 0.05 were considered statistically significant. Data were analyzed using the "SAS 9.1" software (SAS Institute Inc., Cary, NC).

RESULTS

Sixty-eight patients and thirty healthy volunteers were included in the study. There were no patients requiring vasopressor or inotrope support. Baseline demographics and patient characteristics are presented in table 1.

Thirthy-four patients with bacterial meningitis comprised the BM group. The etiology was confirmed in 26 (76.5%) patients. The most common pathogen was *Streptococcus pneumoniae* (12 pts) followed by *Neisseria meningitidis* (7 pts), *Listeria monocytogenes* (4 pts), *Klebsiella pneumoniae* (1 pt), *Enterococcus faecalis* (1 pt) and *Streptococcus agalactiae* (1 pt).

In the NBM group there were 34 patients with non-bacterial meningitis and meningoencephalitis. Disease etiology in 12 patients with viral meningoencephalitis (35.2%) was not confirmed. The most common pathogen in the remaining patients was *Herpes simplex virus* (6 pts), followed by *Tick-borne encephalitis virus* (2 pts), *Cryptococcus neoformans* (2 pts), *influenza A virus* (1 pt), *Mycobacterium tuberculosis* (1 pt), *Epstein-Barr virus* (1 pt), *enterovirus* (1 pt) and *Borrelia burgdorferi* (1 pt). Five patients suffered from postinfectious meningoencephalitis and two patients had acute disseminated encephalomyelitis (ADEM).

The breath-hold period in the control group was 23.3 ± 6.5 seconds (median 23). We found no correlation between BHI_m and the duration of breath-holding (Spearman R 0.108; p=0.623). The possible effect of a too short breath hold to BHI values was thus ruled out.

Advanced age and higher incidence of respiratory failure that required mechanical ventilation were found in the BM group (54 vs. 39 years and 79.4% vs. 50%).

The most prominent difference between BM and NBM patients was the difference in the level of consciousness disturbance (GCS): BM patients had worse scores (GCS 8 vs. 11.5). Therefore, on-admission GCS score was included in the multivariate model analyzing predictivity of BHI for the disease outcome.

Adjuvant steroid treatment was applied in 56% patients with BM according to the current guidelines [2]. Six patients in NBM group received short-term high dose steroids because of severe brain edema (4 pts) and acute disseminated encephalomyelitis (2 pts).

The patients were stratified according to CO_2 reactivity and additional analysis was made. The normal CO_2 reactivity group ("BHI_N") was defined with $BHI_m \geq 1.18$. The impaired CO_2 reactivity group ("BHI_R") was defined with $BHI_m < 1.18$ according to breath-holding indexes in healthy volunteers.

BHI_R group was characterized by advanced age, heavier consciousness disturbance, frequent respiratory failure and often unfavorable outcome in contrast to BHI_N group (table 2). There were no lethal outcomes amongst the 28 patients in BHI_N group.

In patients with BM and normal CO_2 reactivity, we noted a higher incidence of mechanical ventilation, advanced age and heavier consciousness disturbance compared with patients with NBM and preserved CO_2 reactivity (table 2). These findings indicate that in patients with BM neither severe consciousness disturbance nor respiratory failure imply

necessarily the CO_2 reactivity loss. In contrast, unconscious patients with NBM who are mechanically ventilated and have normal CO_2 reactivity are rare (14.2% vs 50%).

There was no significant difference in BHI between patients with bacterial meningitis that received dexamethasone treatment and those who did not. Normal CO_2R was noted in 36.8% (7/19) patients with steroid treatment compared with 46.6% (7/15) in the non-steroid group (p=0.993).

The major indicator of disease severity in patients with CNS infections is GCS [3]. Because of that, the correlation of BHI_m and GCS was analyzed together with other variables which may influence BHI_m. We found that 80.9% (34/42) of all patients with GCS ≤ 10 had impaired CO_2 reactivity. In BM and NBM group that was 76% (19/25) and 88.2% (15/17), respectively.

Univariate regression analysis revealed significant correlation of BHI_m with GCS (ß=0.098; p<0.001), and BHI_m with age (ß= -0.012; p=0.014).

The unfavorable outcome of disease (GOS 1-3) was noted in 28 patients (28/68; 41.1%) (table 3). Nine patients died (five patients in BM and four patients in NBM group) and the overall mortality was 13.2%. The mortality in pneumococcal meningitis was 33.3% (4/12).

The BHI_m was almost identical in GOS 1-3 groups regardless of the etiology (BHI_m median 0.835 in BM versus 0.824 in NBM group).

The comparison of BM and NBM groups according to disease outcome and related BHI_m revealed no significant differences (table 4). Such findings confirmed the BHI_m etiology independence. However, significant differences in BHI_m were noted according to the GOS (Figure 1).

The BHI_m in the favorable group (GOS 4-5) was significantly higher (1.285 vs. 0.835) than in the unfavorable group (GOS 1-3) (table 3). The unfavorable outcome of disease (GOS 1-3) was significantly more frequent in patients with impaired CO_2 reactivity (62.5 vs. 10.7%) (table 2).

Logistic regression analysis was performed in order to establish the prognostic value of BHI_m. The outcome variable was unfavorable outcome (GOS 1-3), while the independent variables were age, GCS and BHI_m. The appropriateness of the fitted model and its predictive utility was confirmed. Patient age and BHI_m showed the strongest influence on disease outcome. A decrease of BHI_m for each 0.1 unit increases the risk of unfavorable outcome by 17%. An increase of age for one year increases the risk of unfavorable outcome by 6% (table 5). These results indicate that BHI_m changes might have a better predictive value than GCS. Receiver operating characteristic (ROC) curve showed that BHI_m has better explanatory value than GCS (AUC 0.785 vs. 0.745).

DISCUSSION

This prospective study assessed cerebrovascular reactivity (CO_2R) by TCD using the breath-holding method in patients with inflammatory CNS diseases. We found that impaired CO_2R is independently associated with the severity and outcome of disease.

The etiology of CNS infection did not show a significant association with chemoregulation loss. However, the etiology was associated with the severity of disease and mechanical ventilation requirement. In patients with BM we found a higher incidence of respiratory failure, advanced age and heavier consciousness disturbance. This finding, however, doesn't imply obligatory chemoregulation loss in these patients. Their grave condition can be explained with reasons outside the CNS such as multiple organ dysfunction/failure due to severe systemic inflammatory reaction and other co-morbidities in older patients. In addition, there were no lethal outcomes in mechanically ventilated patients with normal CO_2R regardless of etiology. The mortality rate in mechanically ventilated patients with impaired CO_2R was similar in both groups (25% vs. 26.6%).

In contrast to previous reports we found no significant influence of adjuvant dexamethasone treatment on CBF chemoregulation recovery [19].

The analysis of BHI according to disease outcome ascertained the association of impaired CO_2R with unfavorable outcome (GOS 1-3). According to literature review, the impaired CBF chemoregulation is almost exclusively confined to bacterial meningitis [9]. That is probably because of particular interest in pneumococcal meningitis patophysiology and the great number of experimental studies [20-24]. The lipid peroxidation and effects of matrix metalloproteinases with consequent endothelial dysfunction seems a plausible explanation. According to our results, the most severe CNS infections result with CO_2R impairment or complete CO_2R loss which was proved to be etiology-independent. The possible mechanisms which could explain the chemoregulation loss in viral and other non-bacterial CNS infections are not known. Intracranial hypertension alone, regardless of cause, can not explain impaired CO_2R. For example, most patients with extreme intracranial hypertension due to cerebral abscess or tumors have normal CO_2R and the use of hyperventilation as well as mannitol infusion results in obvious short-term improvement. A similar response could be seen in patients with bacterial meningitis and preserved CO_2R.

We chose the breath holding method because it proved to be nonaggressive, well tolerated, real-time, reliable and reproducible [15,25]. The lowest BHI_m in our healthy volunteers was similar to previously reported BHI_m by Zavoreo and Demarin (1.18 vs 1.03) [25].

Other methods such as inhalation of 5% CO_2 or acetazolamide injection strongly stimulate vasodilatation of cerebral arterioles [15,26]. Because they also carry the risk of cerebral hyperemia and intracranial hypertension aggravation, these methods are not appropriate for evaluation of cerebral vasoreactivity in patients with severe acute CNS infections. A more advanced techniques to assess the small and medium sized vessel

reactivity such as ASL-MRI (arterial-spin labeled magnetic resonance imaging) and BOLD (blood oxygenation level dependent) imaging are usually unavailable.

A major disadvantage of breath holding method is the necessity for patients' full cooperation if they are not mechanically ventilated. Besides disease severity, the inability of compliance in a proportion of patients is the reason for a relatively high proportion of mechanically ventilated patients in our study (64.7%; 44/68). That is the recognized limitation of our study. The second limitation of the study is a relatively small patient population. This occurred because of strict exclusion criteria and may have resulted in selection bias.

Despite the limitations of our study, our results confirmed the importance of CO_2 reactivity assessment in patients with CNS infections. CO_2R showed good correlation with the severity and outcome of bacterial as well as non-bacterial meningitis. However, the most important value of CO_2R is the capability to define patients with chemoregulation loss immediately upon admission to the hospital. It should be stressed that it is not possible to distinguish these patients by clinical examination or with CT brain scan. The effects of conventional symptomatic treatment (osmotic diuresis, thiopental, hyperventilation) are greatly dependent (or associated with) on cerebral arterioles vasoreactivity [27]. Patients with impaired CO_2R are candidates for therapeutic hypothermia (TH). This life-saving procedure should be started as soon as possible because conventional symptomatic treatment failure and poor outcome of disease in these patients should be anticipated.

Based on the results of this study, we made an internal guideline for TH in patients with severe CNS infections. The major criterion for therapeutic hypothermia is impaired CO_2 reactivity assessed by TCD. In patients without temporal acoustic window, minor criteria [optic nerve sheath diameter ≥ 6.0, GCS ≤ 8 and SjO_2 (jugular bulb venous saturation) < 55% or >75%] are required.

Therapeutic hypothermia during CNS infections may assist with the reduction in cerebral metabolism, cerebral blood volume (CBV), lowering of the intracranial pressure and suppression of the inflammatory host response allowing maintenance of adequate cerebral perfusion pressure. According to our experience, the recovery of CO_2 reactivity cannot be expected before the fourth day of treatment. We recommend the use of TH as soon as possible and at least during the first three days after presentation. The first results of that therapeutic concept in patients with BM are very promising [28]. Therapeutic hypothermia halved the overall mortality in patients with BM and significantly decreased the mortality rates in patients with viral meningoencephalitis at our hospital during the last two years (12% vs. 24% and 9% vs. 20%, respectively - unpublished data).

Our study emphasizes the importance of CO_2 reactivity assessment in patients with CNS infections regardless of etiology. A great predictive value as well as reliable stratification criteria in treatment strategy decision makes this method a very promising tool.

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TABLES

Table 1 Baseline demographic data and characteristics of examinees

	Control group (N=30)	**Bacterial meningitis (BM) (N=34)**	**Non-bacterial meningitis (NBM) (N=34)**	**p-value**
Age (years) median interquartiles	 38 26-55	 54 44-61	 39 25-52	 0.018
Gender male female	 15 (50%) 15 (50%)	 26 (76.5%) 8 (23.5%)	 20 (59%) 14 (41%)	 0.081
GCS median interquartiles	 N/A	 8 6-12	 11,5 6-15	 <0.001
Neurological deficit	N/A	11 (32.3%)	12 (35.2%)	1.000
Steroid treatment	N/A	19 (56%)	6 (17.6%)	0.002
Mannitol infusion	N/A	25 (73.5%)	20 (59%)	0.305
Respiratory failure requiring mechanical ventilation	N/A	27 (79.4%)	17 (50%)	0.022
Mean breath-holding index (BHI_m) median interquartiles range	 1.878 1.513-2.185 1.180-2.996	 1.042 0.675-1.377 0.113-3.02	 1.115 0.736-1.795 0.214-2.857	<0.001[a] 0.389[b]
Glagow Outcome Scale Score (GOS) GOS 1 GOS 2 GOS 3 GOS 4 GOS 5	 N/A	 5 (14.7%) 2 (5.9%) 9 (26.4%) 4 (11.9%) 14 (41.1%)	 4 (11.8%) 0 8 (23.5%) 4 (11.8%) 18 (52.9%)	 0.729

Legend:

[a] BHI_m median: control group vs all patients
[b] BHI_m median: BM vs NBM

Table 2 Characteristics and the outcome of patients according to the CO_2 reactivity

	BHI_N[†]	**BHI_R**[‡]	**p-value**
All patients (N=68)			
N (%)	28 (41.2)	40 (58.8)	N/A
age – years (median)	37	52	0.002
GCS (median)	15	7.5	<0.001
mechanical ventilation N (%)	9 (32.1)	35 (87.5)	<0.001
GOS 1-3 N (%)	3 (10.7)	25 (62.5)	<0.001
mortality N (%)	0	9 (22.5)	0.008
Bacterial meningitis (N=34)			
N (%)	14 (41.2)	20 (58.8)	N/A
age – years (median)	44.5	59	<0.001
GCS (median)	13.5	7.5	0.004
mechanical ventilation N (%)	7 (50)	20 (100)	<0.001
GOS 1-3 N (%)	2 (14.2)	14 (70)	0.004
mortality N (%)	0	5 (25)	0.062
Non-bacterial meningitis (N=34)			
N (%)	14 (41.2)	20 (58.8)	N/A
age – years (median)	29.5	43.5	0.306
GCS (median)	15	7.5	<0.001
mechanical ventilation N (%)	2 (14.2)	15 (75)	0.001
GOS 1-3 N (%)	1 (7.1)	11(55)	0.009
mortality N (%)	0	4 (20)	0.126

Legend:

[†] BHI_N = BHI $\geq$ 1.18 (normal CO_2 reactivity)
[‡] BHI_R = BHI < 1.18 (reduced CO_2 reactivity)

Table 3 Characteristics of the outcome groups

	GOS 1-3 (unfavorable outcome) N=28	**GOS 4-5 (favorable outcome)** N=40	**p-value**
Age (years)			
median	55	39	<0.001
interquartiles	44-65	22-52	
GCS			
median	7.5	13.5	<0.001
interquartiles	4-10	7.5-15	
mechanical ventilation			
N (%)	26 (92.8%)	18 (45%)	<0.001
BHI_m			
median	0.835	1.285	<0.001
interquartiles	0.551-1.044	0.902-1.934	

Table 4 Mean breath holding index (BHI_m) in all patients according to disease outcome

	All patients	GOS 1	GOS 2	GOS 3	GOS 4	GOS 5
All patients						
N (%)	68	9 (13.2%)	2 (2.9%)	17 (25%)	8 (11.7%)	32 (47%)
BHI_m - median	1.069	0.667	0.529	0.983	1.091	1.313
- interquartiles	0.714-1.497	0.291-0.849	0.383-0.675	0.719-1.130	0.826-1.561	1.07-2.082
Bacterial meningitis (BM)						
N (%)	34 (50%)	5 (14.7%)	2 (5.8%)	9 (26.4%)	4 (11.7%)	14 (41.1%)
BHI_m - median	1.042	0.821	0.529	1.020	1.016	1.338
- interquartiles	0.675-1.377	0.341-0.849	0.383-0.675	0.719-1.075	0.641-1.531	1.111-1.673
Non-bacterial meningitis (NBM)						
N (%)	34 (50%)	4 (11.7%)	0	8 (23.5%)	4 (11.7%)	18 (52.9%)
BHI_m - median	1.115	0.479		0.956	1.121	1.312
- interquartiles	0.736-1.795	0.252-0.845		0.668-1.132	0.902-1.800	1.040-2.141

Table 5 Variables associated with unfavorable outcome – logistic regression analysis

Odds Ratio Estimates			
Variable	OR	95% Wald Confidence Limits	
Age	1.063	1.017	1.110
GCS	1.089	0.914	1.298
BHI_m	4.922	1.161	20.875

FIGURES

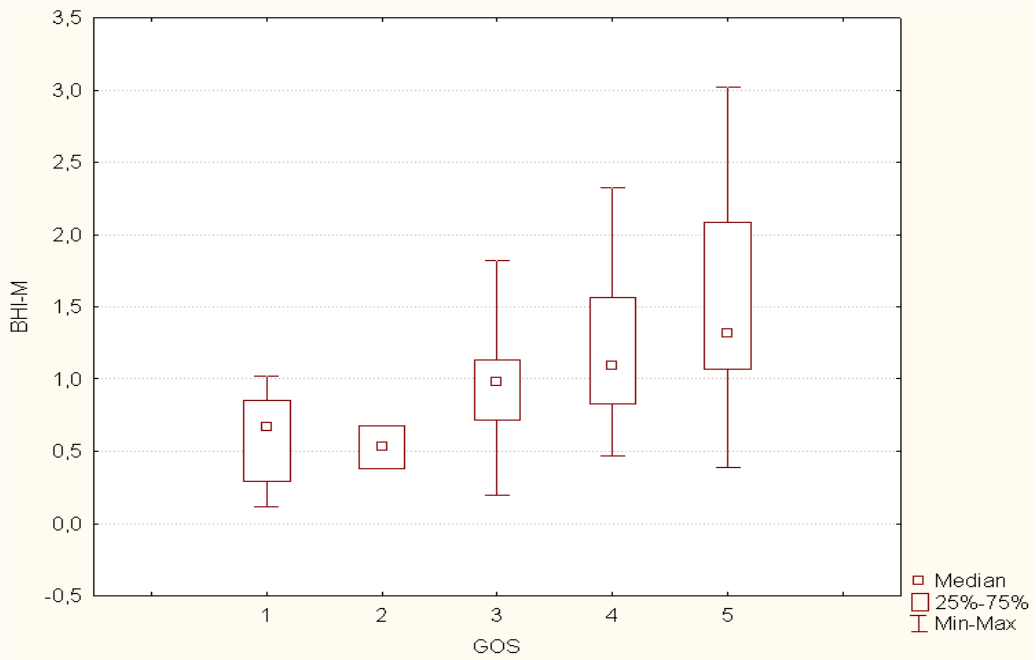

Figure 1. BHI_m according to disease outcome (Glasgow outcome scale score)