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RELATIONSHIP OF NEURON SPECIFIC ENOLASE LEVELS IN SERUM AND CEREBRO SPINAL FLUID WITH COMPLICATIONS AND CLINICAL FOLLOW-UP IN PATIENTS WITH ACUTE BACTERIAL MENINGITIS

ŞADAN HACISALİHOĞLU[1], AHMET ALVER[2], MURAT TOPBAŞ[3], SÜLEYMAN CANER KARAHAN[2], ABDURRAHMAN AVAR ÖZDEMİR[1], FATMA MÜJGAN SÖNMEZ[4,5]

ABSTRACT

Objective: Our aim in this study is to investigate the relationship between serum c-reactive protein levels and cerebrospinal fluid and blood neuron-specific enolase levels in patients with bacterial meningitis.
Materials and Methods: This study was conducted on 22 patients treated with a diagnosis of acute bacterial meningitis. The diagnosis of meningitis was made based on patient history, clinical and laboratory findings. Lumbar puncture was performed on patients at the initial presentation, on days 1 and 7, and on days 15 and 21 if recovery was not observed. The collected samples were analyzed for cell count, culture, Wright and Giemsa staining, protein, glucose and neuron-specific enolase levels. At the same time, serum samples were obtained for the measurement of C-reactive protein and neuron-specific enolase levels. Clinical scoring was performed for all patients at the specified time points.
Results: The mean age of the children in the study was 71±11 months, and 59% were male. All patients presented with fever, with vomiting (77%) and seizures (27%) being the most common additional findings. During follow-up, cerebrospinal fluid protein and leukocyte counts decreased significantly, while glucose levels increased (p=0.002; p=0.025; p=0.06). C-reactive protein levels declined (p=0.012), whereas coma scores increased significantly on day 7 (p=0.046). The baseline cerebrospinal fluid neuron-specific enolase level was 6.08±5.8 µg/L, showing a significant reduction by day 7 (p=0.039); serum neuron-specific enolase levels decreased as well but did not reach statistical significance (p=0.050). At baseline, a positive correlation was observed between cerebrospinal fluid neuron-specific enolase and serum C-reactive protein (r=0.45, p=0.039), but no significant correlation was found on day 7 (r=0.11, p=0.068).
Conclusion: Cerebrospinal fluid and serum neuron-specific enolase levels change with neuronal damage in patients with bacterial meningitis, but no relationship was found between neuron-specific enolase levels and duration of treatment and development of complications.
Keywords: Acute bacterial meningitis, Child, Neuron-specific enolase

AKUT BAKTERİYEL MENENJİTLİ HASTALARDA SERUM VE BEYİN OMURİLİK SIVISINDAKİ NÖRON SPESİFİK ENOLAZ DÜZEYLERİNİN KOMPLİKASYONLAR VE KLİNİK TAKİP İLE İLİŞKİSİ

ÖZET

Amaç: Bu çalışmadaki amacımız; bakteriyel menenjitli hastalarda serum c-reaktif protein ile beyin omurilik sıvısı ve kan nöron spesifik enolaz düzeylerinin ilişkisini araştırmaktır.
Gereç ve Yöntemler: Bu çalışma Eylül 2000 ile Eylül 2001 tarihleri arasında akut bakteriyel menenjit tanısı konarak tedavi edilen 22 hastada gerçekleştirildi. Menenjit tanısı, öykü, klinik ve beyin omurilik sıvısı bulguları ile konuldu. Hastalara başlangıç, 1. ve 7. günlerde ve düzelme olup olmamasına göre 15 ve 21. günlerde lomber ponksiyon yapıldı. Alınan beyin omurilik sıvısı örneklerinden hücre sayımı, kültür, Wright ve Giemsa boyaması, protein, şeker ve nöron spesifik enolaz düzeyleri çalışıldı. Aynı dönemlerde serumdan C-reaktif protein ve nöron spesifik enolaz düzeyleri de ölçüldü. Belirtilen dönemlerde tüm hastalara klinik skorlama yapıldı.
Bulgular: Çalışmadaki çocukların ortalama yaşı 71±11 aydı ve %59 erkekti. Tüm hastalarda ateş mevcut olup, en sık ek bulgular kusma (%77) ve nöbet (%27) idi. Takipte beyin omurilik sıvısı protein ve lökosit sayıları anlamlı şekilde azalırken, glikoz düzeyleri arttı (p=0,002; p=0,025; p=0,06). C-reaktif protein düzeyleri azalırken (p=0,012) 7. günde koma skorları anlamlı olarak yükseldi (p=0,046). Başlangıç beyin omurilik sıvısı nöron spesifik enolaz düzeyi 6,08±5,8 µg/L olup 7. günde anlamlı düşüş gösterdi (p=0,039); serum nöron spesifik enolazda ise azalma olmakla birlikte istatistiksel anlamlılığa ulaşmadı (p=0,050). Başlangıçta beyin omurilik sıvısı nöron spesifik enolaz ile serum C-reaktif protein arasında pozitif korelasyon saptandı (r=0,45, p=0,039), ancak 7. günde anlamlı korelasyon bulunmadı (r=0,11, p=0,068).
Sonuç: Beyin omurilik sıvısı ve serum nöron spesifik enolaz düzeyleri bakteriyel menenjitli hastalarda nöronal hasarla birlikte değişmektedir ancak tedavi süresinin uzunluğu ve komplikasyon gelişimi ile nöron spesifik enolaz düzeyleri arasında bir ilişki saptanamamıştır.
Anahtar Kelimeler: Akut bakteriyel menenjit, Çocuk, Nöron spesifik enolaz

[1]CLINIC OF CHILD HEALTH AND DISEASES, UNIVERSITY OF HEALTH SCIENCES KANUNİ SULTAN SÜLEYMAN TRAINING AND RESEARCH HOSPITAL, İSTANBUL TÜRKİYE
[2]BIOCHEMISTRY, FUNDAMENTAL MEDICAL SCIENCE, FACULTY OF MEDICINE, KARADENİZ TECHNICAL UNİVERSITY, TRABZON,TÜRKİYEPUBLIC HEALTH SCIENCE, FACULTY OF MEDICINE, KARADENİZ TECHNICAL UNIVERSITY, TRABZON,TÜRKİYE
[4]KTU MEDICAL FACULTY, DEPARTMENT OF CHILD NEUROLOGY, RETIRED LECTURER, TRABZON, TÜRKİYE
[5]YUKSEK IHTISAS UNİVERSITY, FACULTY OF MEDICINE, DEPARTMENT OF PEDIATRICS AND CHILD NEUROLOGY, ANKARA, TÜRKİYE

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Sorumlu Yazar: ŞADAN HACISALİHOĞLU
CLINIC OF CHILD HEALTH AND DISEASES, UNIVERSITY OF HEALTH SCIENCES KANUNİ SULTAN SÜLEYMAN TRAINING AND RESEARCH HOSPITAL, İSTANBUL TÜRKİYE

Telefon: +905068323434
E-mail: perpelis@gmail.com

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INTRODUCTION

Acute bacterial meningitis (ABM), a disease characterized by bacterial inflammation of the meninges, continues to be significant in terms of the severity of complications and mortality despite advancements in diagnosis and treatment (1).

Pathogens reach the meninges and proliferate rapidly by crossing the blood-brain barrier through hematogenous spread, direct proximity, or trauma. The inflammatory response initiates the release of chemokines and cytokines, which results in a substantial influx of leukocytes into the affected region. Consequently, while the host's inflammatory response and microglial activation work to eliminate the microorganisms, the severity or prolonged duration of this response may lead to neuronal damage (2-5).

In ABM, the diagnosis is established through morphological, chemical, and microbiological examination of the cerebrospinal fluid (CSF). In ABM, glucose levels in the CSF decrease while leukocyte count and protein levels increase. Elevated CSF leukocyte count and protein levels also indicate damage to the blood-brain barrier (2-4). Although a definitive diagnosis is made by isolating the causative agent in the CSF, this is not always possible. Therefore, CSF's multiplex, panel-based PCR and latex agglutination tests can also identify the pathogen (6,7).

C-reactive protein (CRP) is the most significant protein produced during the acute phase of inflammation, and its concentration in the blood is generally proportional to the severity of bacterial infection. Elevated serum and CSF CRP levels favor bacterial infection, especially in distinguishing bacterial meningitis from viral meningitis (8,9). While existing markers help diagnose ABM, their utility in assessing the severity of inflammation, neuronal damage, and potential complications remains limited.

Neuron-specific enolase (NSE) is an enolase isoenzyme known as gamma enolase, found in mammals. It has a molecular weight of 80,000 daltons. Gamma enolase is present in cells of neuronal origin and mature neurons, as well as in peripheral tissues and lymphocytes in small amounts. The transition of NSE from alpha to gamma subunits is a late event in neuronal differentiation, and the gamma subunit is a marker for all neuron types and all neuroendocrine and para-neuronal cell types in the periphery. Therefore, the formation of NSE is a reliable marker for neuronal maturation (10,11).

In diseases such as Alzheimer's, Huntington's chorea, and Amyotrophic Lateral Sclerosis (ALS), increased levels of NSE have been detected in the CSF and serum. In Parkinson's disease, acute or chronic progressive neurological disorders, and neuroendocrine cancers, serum and CSF NSE levels have helped assess damage, prognosis, and treatment monitoring (12-14). These studies suggest that measuring brain biomarkers such as NSE may be beneficial in predicting the severity of meningitis infections, the development of subclinical lesions, and potential complications.

This study aims to investigate the relationship between serum CRP levels and CSF and blood NSE levels with the clinical course of the disease and the complications that arise during the acute phase and follow-up period in patients with bacterial meningitis.

MATERIAL AND METHODS

This prospective study, conducted between September 2000 and September 2001 at the Department of Pediatrics, Faculty of Medicine, Karadeniz Technical University, involved 22 hospitalized patients diagnosed with ABM. The Faculty of Medicine Ethics Committee approved the study (Approval no: 99.114.003.2), and written informed consent was obtained from the parents of all children.

The study excluded newborns, patients over 17, those with congenital or chronic diseases, those who had previously received antibiotic treatment, patients with uncertain diagnoses, and those whose parents did not consent.

The diagnosis of ABM was made based on patient history, clinical CSF findings (cell count and type, protein, and glucose levels), Gram staining, culture and latex agglutination tests to detect specific bacterial antigens. Lumbar puncture (LP) was performed on patients at the initial presentation, on days 1 and 7, and on days 15 and 21 if recovery was not observed. The collected CSF samples were analyzed for cell count, Wright and Giemsa staining, protein, and glucose levels. In our study, CSF samples were evaluated for hemolysis, and the presence of more than 5 red blood cells/mm^3 or a macroscopically hemorrhagic appearance of the sample was considered as hemolysis. Hemolysis thresholds and

erythrocyte counts of the CSF samples were regularly assessed. CSF samples were stored at -20°C to evaluate NSE levels. Simultaneously, 2 cc of serum were collected before each LP and sent to the laboratory to measure blood glucose, serum CRP, and NSE levels.

In addition to obtaining CSF cultures from each patient, specific bacterial antigens for *H. influenza* type b, *S. pneumoniae*, and *N. meningitidis* type A, B, and C were investigated using the Slidex meningitis latex agglutination kit (Lot: 742434701, 1445 brand), and positive control tests were performed. CRP levels were measured using the nephelometric method with the Behring Nephelometer BN II device and its corresponding kits. CSF and serum glucose levels were analyzed using the glucose oxidase (GOD)-peroxidase (POD) method on the Roche Diagnostic modular device. CSF protein levels were measured with the Vitros (Johnson & Johnson) device using a colorimetric method. NSE levels in serum and CSF samples were manually analyzed using the ELISA Prolifigen® NSE IRMA method (Lot: 324560).

All patients underwent physical and neurological examinations at the initial presentation, on days 1, 7, and 15, and for those with prolonged treatment, on day 21. Consciousness was assessed using the Simpson & Reilly Pediatric Coma Scale (15). For patients who experienced seizures, EEG recordings were performed using a Nihon Kohden 14-channel EEG device with a 10-20 electrode system. During follow-up, necessary biochemical and radiological evaluations, such as computed tomography (CT) and magnetic resonance imaging (MRI), were performed in cases of clinical conditions like brain edema, subdural effusion, electrolyte imbalances, seizures, and feeding disorders.

In all cases, empirical therapy was initiated with ceftriaxone, and the regimen was adjusted according to culture/antibiogram results and infectious diseases consultation. In cases of insufficient clinical response, persistent pathology in biochemical markers, and/or ongoing radiological findings, the duration of treatment was extended up to 15–21 days; the duration was individualized according to the causative agent and clinical course (2,16).

Statistical Methods

Descriptive data were presented as mean ± standard deviation and percentages (%). Data conformity to a normal distribution was evaluated using the Kolmogorov-Smirnov test for each group. Analysis of Variance (ANOVA) (with Paired t-test as a post hoc analysis) and the Student's t-test were used for variables following a normal distribution. Variables that did not follow a normal distribution were analyzed using the Friedman test (with the Wilcoxon test as a post hoc analysis) and categorical data were evaluated with the chi-square test. The relationship between variables was assessed using Pearson correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The ages of the 22 patients included in the study ranged from 2 months to 13 years (71 ± 11 months); 13 were male (59%) and nine were female (41%). The most common presenting complaint was fever; all 22 patients (100%) had a fever of 38°C or higher. Other presenting symptoms included vomiting in 17 patients (77%), convulsions in 6 patients (27%), and a rash in 5 patients (23%). On physical examination, Kernig's sign was found in 11 patients (50%), Brudzinski's sign in 8 patients (36%), papilledema and opisthotonus in 2 patients (9%), and bulging fontanelle in 1 patient (5%) (Table 1).

Table 1. Symptoms and Clinical Findings of Patients

Symptom/Clinical Finding	Patient Count (n, %)
Total Patients	22 (100)
Gender	
- Male	13 (59)
- Female	9 (41)
Fever	22 (100)
Vomiting	17 (77)
Kernig's Sign	11 (50)
Brudzinski's Sign	8 (36)
Seizures	6 (27)
Rash	5 (23)
Papilledema	2 (9)
Opisthotonus	2 (9)
Fontanel Bulging	1 (5)

The average CSF protein levels of the patients were as follows:

Day 0: 172.70 ± 116.20 mg/dl; Day 1: 113.00 ± 85 mg/dl; Day 7: 70.40 ± 60 mg/dl. For the six patients with prolonged treatment, the value on Day 15 was 53.83 ± 50.15 mg/dl.

The decrease in protein levels on days 1, 7, and 15 was statistically significant compared to the baseline (p=0.002). CSF glucose levels showed a significant increase on days 1 (62.60 ± 22.2) and 7 (61.10 ± 18.1) compared to baseline (43.50 ± 30.5) (p=0.025). The CSF leukocyte count was as follows: Day 0: 3464/mm^3; Day 1: 1942/mm^3; Day 7: 49/mm^3. The leukocyte count at days 1, 7, and 15 showed a significant decrease compared to the baseline, similar to the protein levels (p=0.06). Post-hoc test revealed that the difference was attributable to day 0 in comparison with the other days (Table 2).

Table 3 shows the significant changes observed over time in CSF protein, glucose, and leukocyte counts in patients undergoing prolonged treatment. Compared to baseline, protein and leukocyte counts decreased, whereas glucose levels increased, and these differences were statistically significant (p=0.04, p=0.032, p=0.042). Post-hoc analysis revealed that the difference in protein and glucose levels originated from day 0, while the difference in leukocyte levels originated from days 0 and 15 (Table 3).

Culture growth was observed in the CSF of five patients, and in two patients (9%), *S. pneumoniae* was identified; in one patient (5%), *H. influenza* was found, and in two patients (9%) *N. meningitidis* was detected. In the examination of 22 patients using the latex agglutination kit, *H. influenza* was found in 13 patients (59%), *N. meningitidis* in 6 patients (27%), and *S. pneumoniae* in 3 patients (14%). The same pathogens identified in the culture were also detected in the latex test of the five patients with positive culture growth.

The initial coma score of the patients included in the study was 12.4±1.20, which increased to 13.3±0.8 on day 1 and 13.8±0.4 on day 7. This increase was statistically significant (p<0.05). It was determined that the initial coma score of the six patients with prolonged treatment was significantly lower than that of the other 16 patients (p=0.046). The serum CRP levels of the patients were 8.70±8.0 mg/dl at baseline, 7.60±8.20 mg/dl on day 1, and 2.40±4.30 mg/dl on day 7. The decrease between the baseline and day 7 values was statistically significant (p=0.012). When the CSF NSE levels of the 22 patients were examined, it was observed that the initial level was 6.08±5.80 µg/L, which decreased to 4.00±5 µg/L on day 1 and 3.60±4.20 µg/L on day 7. A statistically significant decrease in the values on days 1 and 7 compared to the baseline was observed (p=0.039). Post-hoc test showed that the difference was attributable to day 0 and day 7 values.

Tablo 2. CSF Glucose, Protein, and Leukocyte Counts of Patients

	Day 0 (n=22)	Day 1 (n=22)	Day 7 (n=22)	Day 15 (n=6)	Day 21 (n=1)	**p**
Protein (mg/dl)	172.7±116.2[a]	113.0±85.0[b]	70.4±60.0[c]	53.8±50.1	52.6	0.002[f]
Glucose (mg/dl)	43.5±30.50[d]	62.6±22.2[e]	61.1±18.1[f]	62.3±20.8	53	0.025[f]
Leucocyte (mm^3)	3464±4588[g]	1942±3282[h]	49±106[ı]	15±5.0	20	0.006[f]

f: Friedman
Post-hoc test (Wilcoxon): a-b (p=0.011), a-c (p=0.002), g-h (p=0.051), g-ı (p=0.003), h-ı (p=0.001)

Tablo 2. CSF Glucose, Protein, and Leukocyte Counts of Patients

	Day 0 (n=6)	Day 1 (n=6)	Day 7 (n=6)	Day 15 (n=6)	Day 21 (n=1)	**p**
Protein (mg/dl)	261.83 ± 89.6[a]	[1]21.83 ± 109[b]	92.16 ± 86.27[c]	53.83 ± 50.1[d]	52.6	0.004[f]
Glucose (mg/dl)	30.33 ± 26.06[e]	62.00 ± 19.5[f]	70.20 ± 21.60[g]	62.33 ± 20.8[h]	53	0.032[f]
Leucocyte (mm^3)	5138 ± 5326[ı]	3498 ± 4353[i]	860 ± 193[j]	15 ± 5.0[k]	20	0.042[f]

f: Friedman
Post-hoc test (Wilcoxon): a-b (p=0.031), a-c (p=0.030), a-d (p=0.030), e-f (p=0.035), e-g (p=0.030), e-h (p=0.035), ı-j (p=0.041), ı-k (p=0.028), i-j (p=0.030), i-k (p=0.029), j-k (p=0.031).

Serum NSE levels of 22 patients were evaluated using blood samples collected simultaneously with CSF NSE. However, due to hemolysis in 12 samples, only the remaining 10 patients' serum NSE levels could be analyzed. The mean serum NSE levels were 12.40±6.40 µg/L at baseline, 11.10±5.70 µg/L on day 1, and 7.80±5.40 µg/L on day 7. The day 7 serum NSE value was lower compared to baseline and day 1 values, showing a borderline statistical significance (p=0.05) (Table 4).

In the six patients undergoing prolonged treatment, the mean coma score on day 0 was found to increase by day 15, while CRP and CSF NSE levels decreased. These differences were statistically significant (p=0.035, p=0.030, p=0.024). However, although serum NSE levels decreased, the difference was not significant. The fact that this group included only four patients made it difficult to evaluate the difference (Table 5). When patients undergoing prolonged treatment were compared with those receiving standard treatment duration, no significant difference was found in baseline and day 7 CSF NSE (p=0.55, p=0.46) and serum NSE values (p=0.60, p=0.42).

At baseline, a positive correlation was observed between CSF NSE levels and serum CRP values (r=0.45, p=0.039), whereas non-significant correlation was found between their values on day 7 (r=0.11, p=0.068). Non-significant correlation was observed between CSF NSE and coma score (r=0.12, p=0.070) or between CSF NSE and serum NSE levels (r=0.18, p=0.069). In addition, there was non-significant correlation between serum NSE and CRP levels (r=0.15, p=0.082).

Among the patients with prolonged treatment, the treatment of one patient was extended to 21 days. The coma score on the 21st day of this patient was 14, and the CRP, CSF, and serum NSE levels were 0.35 mg/dL, 7.2 µg/L, and 7.8 µg/L, respectively. Both CSF and serum NSE levels were higher compared to baseline, and the patient had complications, including left peripheral hearing loss, as well as widespread and severe background rhythm disturbance on EEG and an epidural abscess.

Table 4. The average scores, CRP, and NSE levels of the patients

	n	Day: 0	Day: 1	Day: 7	**p**
Score	22	12.40±1.20[a]	13.30±0.80[b]	13.80±0.40[c]	0.046[f]
CRP mg/dl	22	8.70±8.0[d]	7.60±8.20[e]	2.40±4.30[f]	0.012[f]
CSF NSE µg/L	22	6.08±5.80[g]	4.00±5.00[h]	3.60±4.20[i]	0.039[f]
Serum NSE µg/L	10	12.40±6.40[i]	11.10±5.70[j]	7.80±5.40[k]	0.050[f]

f: Friedman
Post-hoc test (Wilcoxon): a-c (p=0.040), d-f (p=0.005), g-l (p=0.037), I-k (p=0.027)

Table 4. The average scores, CRP, and NSE levels of the patients

	n	Day: 0	Day: 1	Day: 7	Day: 15	**p**
Score	6	11.83±0.75[ı]	13.16±0.75[i]	13,66±0.81[j]	14±00[k]	0.046[f]
CRP mg/dl	6	9.54±9.17[l]	9.73±10.03	2.08±1.90	3.36±3.31[n]	0.012[f]
CSF NSE µg/L	6	4.80±3.03[o]	3.74±3.50	4.75±6.70	0.70±0.30[p]	0.039[f]
Serum NSE µg/L	4	14.50±8.80	11.56±8	10.75±10.20	8.70±3.70	0.050[f]

f: Friedman
Post-hoc test (Wilcoxon): ı-k (p=0.031), l-n (p=0.022), o-p (p=0.043)

Complications developed in 4 of the following patients. One patient had an epileptic focus, and the second patient had widespread background activity disturbance and minimal dilation of the third ventricle; the third patient had left peripheral hearing loss, a previous epidural abscess, and widespread background activity disturbance. In contrast, the fourth patient had dural-based opacification, hydrocephalus, and a millimetric nonspecific lesion in the right cerebellar hemisphere.

When the data of patients who developed complications were examined, it was observed that, similar to the other patients, protein levels, leukocyte counts, and CSF and serum NSE levels at baseline were higher compared to day 7, while glucose levels were lower. The number of patients who developed complications was not sufficient to perform a valid statistical analysis (Table 6).

The effect size of this study was calculated using Kendall's W test. The effect sizes for CSF protein, leukocyte count, and glucose were moderate to high (W = 0.6, 0.46, and 0.49, respectively). However, for NSE, Kendall's W was 0.25, indicating a small effect size. The relatively small sample size, particularly in subgroup analyses, limited the statistical power of the study.

DISCUSSION

In this study, CSF NSE levels in patients with acute bacterial meningitis were found to be significantly elevated at baseline and showed a marked decrease during the course of treatment. Although a decrease was also observed in serum NSE levels, this change was not statistically significant. No significant relationship was found between NSE levels and the development of complications, the duration of treatment, or clinical scores.

The diagnosis and follow-up of meningitis predominantly rely on clinical symptoms and findings, along with CSF analysis that includes protein, glucose, cell type, and count (1,7). Various markers such as lactate, CRP, granulocyte elastase, total amino acids, lactoferrin, lactate dehydrogenase, and its isoenzymes have been studied for use in the diagnosis of meningitis; however, none of these are sufficient (17-20). Studies have shown that if the hypoxic condition in the tissue persists in bacterial meningitis, cellular necrosis occurs, and during this process the concentration of NSE in the CSF increases. NSE levels, as an indicator of neuronal injury, can provide insights into the biochemical disturbances that occur during meningitis (20,21).

Table 6. Values of patients with complications

	n	Day:0	Day:1	Day: 7
Protein mg/dl	4	202±105	115.5±97.3	92.5±83
Glucose mg/dl	4	34.30±27	60±30	63±25.5
Leukocytes mm^3	4	3441±5082	1960±3580	821±1949
Score	4	12.3±1.36	13.3±0.81	13.66±0.81
CRP mg/dl	4	7.85±10.10	6.85±9.30	1.30±1.8
CSF NSE µg/L	4	4.00±2.5	2.30±2.90	2.80±2.80
Serum NSE µg/L	4	12.6±9.3	9.30±8.20	8.80±8.00

Enolase is a glycolytic enzyme found in various tissues. It is a dimeric protein with α, β, and ɤ subtypes. The αα subtype is found in the liver and glial cells, ββ and αβ in skeletal and cardiac muscle, and ɤɤ and αɤ in neurons and the peripheral neuroendocrine system (22,23). Due to its release into the CSF during hypoxic conditions, NSE was initially considered a potential marker primarily in brain trauma. Subsequently, various studies were conducted on adults with primary and secondary neurological diseases. These studies indicated that CSF NSE levels tended to be elevated in patients with cerebral infarction, status epilepticus, craniocerebral trauma, and heart failure, and that such increases may be associated with the severity of damage and prognosis (23-27).

When performed under appropriate conditions, the determination of CSF NSE levels may serve as a marker for assessing neuronal injury and short-term prognosis in cases of acute childhood encephalopathy (28).In a study conducted by Bartek et al. on adult patients with ABM, it was found that NSE levels were also elevated (peak level of 13 µg/L) in patients with impaired neuronal metabolism and a high Lactate/Pyruvate (L/P) ratio. The correlation between increased L/P ratio and NSE suggests that excessive anaerobic conditions in the brain affect neurons (29). In a study by Thornberg et al. on newborns with hypoxic-ischemic encephalopathy, CSF NSE levels were 10.0 µg/L in the control group and 25.4 µg/L in the patient group (30).

Inoue et al. evaluated CSF NSE levels in 10 patients with ABM between 3 months and 3 years, at baseline and on the 2nd and 10th days of treatment. They found that CSF NSE levels were higher in patients with bacterial meningitis. They observed that patients with levels exceeding 25 µg/L developed subdural effusion and sequelae, suggesting that CSF NSE levels could be a good indicator of neurological complications and follow-up (31). In our study, on days 0, 1, 7, and 15, only one patient had a CSF NSE level of 22 µg/L in the acute phase, and no clinical complications were observed.

In a study conducted by Nara et al. on children with acute encephalitis, it was reported that normal CSF NSE levels were below 9.1 µg/L. Still, NSE levels increased as the comatose state and damage severity worsened (32). Similarly, in a study by Rodríguez et al., the average CSF NSE level in 37 healthy children was found to be 1.52±1.1 µg/L, and they suggested that CSF NSE levels below 5 µg/L should be considered normal (33). In the study conducted by Alam et al., the mean CSF NSE level in healthy children was reported as 1.69 ± 0.91 ng/mL, whereas values reached 20.19 ± 2.02 µg/L in viral meningitis and 50.50 ± 8.96 µg/L in bacterial meningitis (34). In the study by Somer et al., the mean CSF NSE level in pediatric meningitis cases was 18.4 ± 12.3 µg/L, while the mean serum NSE level was 32 ± 19.8 µg/L. In the control group, the mean CSF NSE level was 2.6 ± 1.1 µg/L and the mean serum NSE level was 10.1 ± 3.4 µg/L (35). These findings support the hypothesis that meningitis infections cause neuronal injury, leading to increased NSE concentrations.

In another study by Rodríguez et al., involving 45 bacterial, 46 viral, and nine tuberculous meningitis patients aged between 1 month and 13 years, along with 160 controls, CSF levels of NSE, nucleotides, purine bases, oxypurines, and uric acid were evaluated. They found that CSF ATP breakdown products were significantly higher in children with bacterial meningitis compared to controls; however, contrary to the findings of Inoue et al., NSE levels were found to be low (36). Various researchers have explained this by suggesting that in the early phase of meningitis, hypoxia may not occur with the intensity and duration necessary to cause cell lysis and subsequent NSE release (32,37).

In our study, when all patients were evaluated, baseline CSF NSE levels were found to be on average 6.08 ± 5.8 µg/L, with a significant decrease observed on days 1 and 7 of treatment. NSE levels were above 5 ng/mL in 11 cases (7 at baseline and four on the 1st day). Complications were observed in 2 of these patients. However, in one patient with an elevated level of 22 µg/L in the acute phase, no complication was observed. The mean values in our study were higher than those reported by Rodríguez et al. in healthy children, but they were not as high as those reported in bacterial meningitis series in the literature (33-35). These results support that NSE levels increase in bacterial meningitis, but also indicate that they may vary across different patient groups. Inoue et al. reported that patients with very high NSE levels developed sequelae, while Nara et al. suggested an association between high levels and both coma state and severity of damage in children (31,32). These findings suggest that NSE levels may be useful in monitoring neurological complications. However, in our study, baseline values were lower in patients who developed complications and required prolonged treatment compared to other patients, and no direct relationship was found between NSE levels and treatment duration or development of complications. In addition, no correlation was found between NSE levels and coma scores. Therefore, it does not appear possible to directly associate NSE levels with the clinical course.

Although there are studies investigating CSF NSE levels in pediatric meningitis patients, studies examining serum NSE levels are limited and often involve comparative studies with other neurological diseases. Ko FJ et al. investigated CSF and serum NSE levels in children with various neurological diseases and found elevated serum NSE levels in only 2 out of 21 meningitis cases (38). In a study by Lima et al., which included older age groups (13–82 years), CSF and serum NSE levels were analyzed, and it was observed that serum NSE levels did not correlate with CSF NSE levels. The same study also found that patients with lower Glasgow Coma Scale scores had higher CSF NSE levels and concluded that CSF NSE is not specific for detecting neuronal damage based on these findings (39). Consistent with the results of these two studies, our study also found no correlation between CSF NSE and clinical scores or serum NSE levels.

Our study has several limitations. First, the relatively small number of patients limited statistical power in subgroup analyses. Second, NSE measurements were not possible in 12 serum samples due to hemolysis, limiting the serum analyses. Furthermore, our study was conducted at a single center, which limits the generalizability of the results. Therefore, further studies are needed to evaluate the limitations of this study.

In summary, our findings demonstrate that CSF NSE levels are elevated in pediatric patients with acute bacterial meningitis, consistent with previous studies. However, no significant association was found between NSE levels and clinical scores, treatment duration, or the development of complications. Serum NSE levels were not correlated with CSF NSE levels, supporting the notion that serum measurements cannot replace CSF analysis. The variability observed across studies suggests that NSE may not fully reflect the extent of neuronal damage. These limitations indicate that larger, prospective studies are needed to clarify the diagnostic and prognostic value of NSE in meningitis.

Acknowledgement

The authors declare no conflicts of interests.

Ethical Consideration

The Faculty of Medicine Ethics Committee approved the study (Approval no: 99.114.003.2), and written informed consent was obtained from the parents of all children.

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