ISSN: 2755-0133

Journal of Medical & Clinical Nursing

Research Article

Open Access

Predictive Values of CSF Ferritin in Cognitive Assessment of Patients after Acute Central Nervous System Infections

Belma Gazibera[1,4*], Lejla Haračić[2], Enra Mehmedika-Suljić[3,5], Selma Šabanagić-Hajrić[3,5], Meliha Hadžović - Čengić[1], Rusmir Baljić[1,4,5], Refet Gojak[1,5], Adna Mustedanagić[1], Ajnur Hadžiahmetović[1] and I Aldin Karić[1]

[1]Department of Infectious Disease, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

[2]Department of Psychiatry, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

[3]Department of Neurology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

[4]Faculty of Health Care, University "Džemal Bijedić" Mostar, USRC "Midhad Hujdur Hujka", Sjeverni logor, 88000 Mostar

[5]Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina

ABSTRACT

CNS infections represent a unique challenge to clinicians due to significant morbidity and mortality. The role of ferritin as a reactant of various pathological conditions is currently being intensively investigated. The pathogenesis of cognitive impairment after acute neuroinfectious disease is not yet fully understood. It is believed to be a direct consequence of neuronal damage by the infection, but also by the activation of immunocompetent brain cells, with consequent disruption of signal conduction in a varying period of time after the infection has resolved.

The aim of the study is to examine the prediction of ferritin on the degree of cognitive impairment in patients who have suffered from a CNS infection. The values of CSF ferritin were evaluated in three analyzed groups of subjects (bacterial, viral and group with normal CSF findings - meningism). The analyzed clinical data were correlated with the degree of neurocognitive impairment, and the relationship between CSF ferritin and the degree of cognitive impairment was analyzed.

The conducted research is a retrospective-prospective analytical and clinical study that was conducted in the period from 01.01.2017 to 01.01.2020. The research includes 90 patients according to previously nominated criteria, divided into three groups, two "examined" and one "control". The assessment of the cognitive status of the subjects was performed using the MMSE test. The SPSS for Windows software package (version 20.0, SPSS INC, Chicago, Illinois, USA) was used for statistical analysis of the obtained data.

We confirmed that the CSF protein ferritin is a good predictor of distinguishing purulent from viral meningitis / meningoencephalitis. The obtained results did not confirm the hypothesis that elevated CSF ferritin values have a negative impact on cognition. Impairment of individual domains of cognition measured by MMSE I, such as "attention", "calculation" and "memory" are more pronounced in purulent CNS infections. Impairment of individual domain MMSE II "calculation" is more pronounced in the purulent CNS infection category.

***Corresponding author**

Belma Gazibera, 1Department of Infectious Disease, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina, 4Faculty of Health Care, University "Džemal Bijedić" Mostar, USRC "Midhad Hujdur Hujka", Sjeverni logor, 88000 Mostar.

Received: July 15, 2025; **Accepted:** July 22, 2025; **Published:** September 05, 2025

Introduction

Central Nervous System (CNS) infections present a unique challenge to clinicians due to their significant morbidity and mortality. The risk of long-term sequelae that persist after the acute illness has resolved makes early recognition and confirmation of the diagnosis imperative [1]. There are a large number of clinical entities that fall into this health field, and according to the localization of the inflammatory process, the most important are: acute meningitis (AM), encephalitis, meningoencephalitis, and focal infections such as abscess or subdural empyema [2]. Patients with neurodegenerative, neurobehavioral, and psychiatric diseases usually have some of the bacterial or viral CNS infections as an introduction to the disease [3]. Clinical manifestation in the initial phase of the disease, when meningeal signs and symptoms are pronounced, is a consequence of pathophysiological events such as: increased BBB permeability, impaired brain metabolism, and impaired cerebral blood flow [4]. The main bacterial agents that cause AM in all age groups are Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenza [5]. The treatment of bacterial AM implies the use of antimicrobial therapy in order to eradicate the causative agent, but also the prevention and treatment of complications of this disease [6].

The most common viruses that cause acute CNS infections are: HSV, Enteroviruses, VZV, EBV (Ebstein-Barr virus - EBV), measles and arboviruses [7]. Diagnosis of a specific virus reduces the unnecessary use of antiviral drugs [8]. The gold standard for etiological differentiation of CNS infections is CSF analysis, starting from macroscopic findings in terms of color and pressure, to chemistry analysis and culture [9].

Ferritin is a protein found in all cells of the body and is responsible for storing iron. Very small amounts are found in the serum, which reflects good storage in healthy individuals [10]. The role of ferritin as a reactant in various pathological conditions is currently being intensively investigated. Elevated serum levels occur in conditions such as acute or chronic inflammation, chronic alcohol consumption, liver disease, renal failure, metabolic syndromes or malignancy [11]. The effects of ferritin during bacterial CNS infection are a consequence of: increased BBB permeability and the penetration of serum ferritin where it is synthesized as a reactant of acute inflammation, synthesis in inflammatory cells of the brain, secretion from ischemic and necrotizing nerve cells affected by the inflammatory process [12].

The pathogenesis of cognitive impairment after acute neuroinfectious disease is not yet fully understood. It is believed to be a direct consequence of neuronal damage by infection, but also by activation of immunocompetent brain cells, with consequent disruption of signal conduction in a variable period after the infection has resolved [13]. Objective assessment of cognitive impairment involves the use of one or more standardized tests for neuropsychological assessment. The Mini-mental state examination (MMSE), the Montreal Cognitive Assessment Test (MoCA) or the Mini Cognitive Test (Mini-Cog test) are some of the tests for examination, which are specific enough to examine dementia, but not enough for mild cognitive impairment [14]. The MMSE is a useful tool, but the examination of patients should be on an individual basis and in a broader context, including personality characteristics, education, behavior and functioning in the community. A symptomatic patient with already pronounced dementia or cognitive impairment may have a cut-off point on the MMSE scale of 17 points according to some studies, but with a lower sensitivity rate [15].

Objective

The aim of the study is to examine the predictive power of CSF ferritin on the impact of the degree of cognitive impairment in patients who have suffered from a CNS infection.

Material and Methods

The study is a retrospective-prospective analytical and clinical study conducted in the period from 01.01.2017. to 01.01.2020. The data used are part of the regular diagnostic and therapeutic protocols in the treatment of patients diagnosed with acute CNS infection, which were carefully recorded in each individual medical history and temperature list. Adult patients who had CSF sampled and CNS infection was proven, patients who had CSF sampled due to clinical suspicion of CNS infection, but it was normal (meningism), were included. The study did not include patients who were prevented from coming for check-ups and thus prevented from MMSE monitoring in the planned follow-up period.

The study included 90 patients divided into three groups, two “test” and one “control”. The test groups were treated according to the protocols of CNS infections, while the control group was guided by the diagnostic and treatment guidelines for patients with the diagnosis of “Fever of Unknown Origin” (FUO). The entire sample was divided into three groups: the first “test” group, 30 subjects, those with a positive CSF finding in the sense of acute purulent CNS infection, the second “test” group, 30 subjects, those with a positive CSF finding in the sense of acute serous CNS infection, the third “control” group, 30 subjects, those who were managed as meningism, with normal CSF findings. The following demographic parameters were analyzed: age and gender, duration of illness before admission measured in hours, pre-hospital treatment (antibiotics, antivirals), length of hospitalization measured in days, treatment outcome characterized as cured and cured with sequelae, types of sequelae: physical (weakness of extremities, hypotonia, hydrocephalus), neurological (epilepsy, paresis) and psychological (cognitive dysfunction). Cohorting into the two study groups was performed based on the value of pleocytosis and the number of Lkc in CSF. Ferritin concentration in CSF was expressed in ng/mL.

The cognitive status of the subjects was assessed using the MMSE test, which is the most commonly used psychometric method. Testing of the subjects lasted between 5 and 10 minutes. Using 11 questions of this test, the following functions were examined: orientation in time and space, attention, calculation, memory, language, ability to execute simple commands [16]. Scoring was on a scale of 0 to 30. Possible cognitive impairment was recorded with a score of 23 or lower. This score indicates the need for a detailed assessment. It is universally applicable, regardless of age group, education, race group, or the like [17].

The SPSS for Windows software package (version 20.0, SPSS INC, Chicago, Illinois, USA) was used for statistical analysis of the obtained data.

The Results

The age limit is comparable for all three examined categories. Patients with purulent CNS infection have an average age of 49.73±21.15 years, while those with a viral infection have an average age of 35.73±15.59 years. Patients with meningism have an average age of 41.37±20.53 years.

The average time of illness until hospitalization (measured in hours) for subjects with purulent CNS infection is 19.00 (11.5-50.00) hours, for subjects with viral 24.00 (14.75-73.50) hours, and for those with meningism 63.0 (16.50-123.50) hours. There is a significant deviation for the category of meningism in relation to the two examined categories.

Patients with purulent CNS infection had the longest hospital stay with a duration of 29.00 (17.5-43.50) days compared to those with viral infection 14.50 (13.75-22.00) and meningism 11.00 (8.75-18.75) days (Table 1).

Table 1: Demographic Characteristics: Age, Duration of Illness, Length of Hospitalization

	CNS infection	Number (N)	Mean value	Standard deviation	Minimum	Maximum	Median
Age	1*	30	49,73	21,15	18,00	90,00	52,50
	2**	30	35,73	15,59	18,00	69,00	34,50
	3***	30	41,37	20,53	18,00	85,00	35,50
Length of illness until hospitalization (measured in hours)	1*	30	30,33	26,28	3,00	85,00	19,00
	2**	30	55,93	60,68	5,00	240,00	24,00
	3***	30	111,23	174,22	4,00	850,00	63,00
Length of hospitalization (measured in days)	1*	30	32,53	16,67	11,00	65,00	29,00
	2**	30	17,50	7,60	6,00	41,00	14,50
	3***	30	13,83	8,35	1,00	36,00	11,00

* purulent CNS infection, ** viral CNS infection, *** meningism

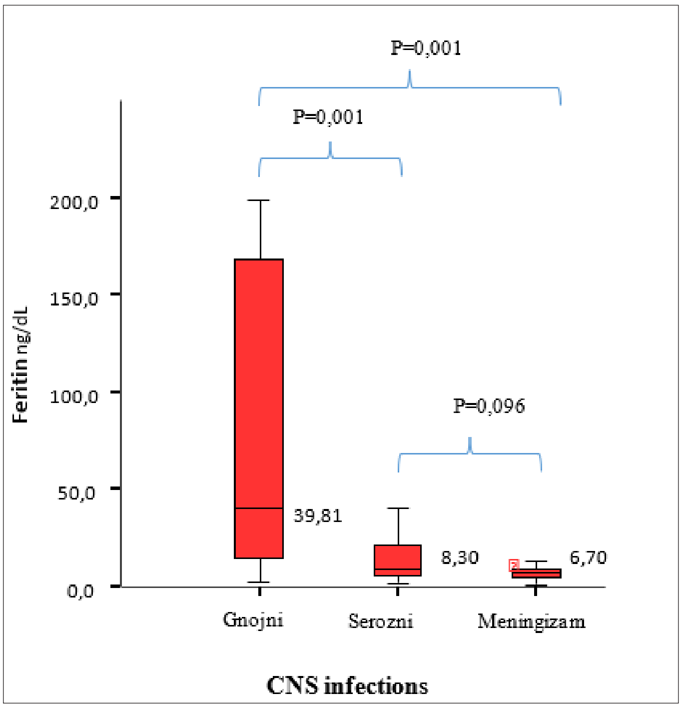
The average ferritin value of subjects with purulent CNS infection is 39.81 ng/dL (14.19-175.70), in viral CNS infection 8.30 ng/dL (5.30-20.43), while in patients with meningism it is 6.70 ng/dL (4.16-8.33) (Table 2).

Kruskal Wallis Test showed that there is a statistically significant difference in the average values of CSF ferritin between the studied groups, p=0.0001 $\chi 2=27.64$. Mann-Whitney U test showed that these differences were not statistically significant between the serous CNS infection and meningism groups, p=0.096 (Graph 1).

Table 2: Descriptive Statistics: Average Values of CSF Ferritin

Ferritin (ng/dL)	1*	30	269,72	535,24	2,62	2253,00	39,81
	2**	30	18,40	26,29	1,90	129,60	8,30
	3***	30	10,96	17,79	1,20	98,50	6,70

*bacterial CNS infections, ** viral CNS infections, *** meningism



Graph 1: Average Values of Ferritinorrhagia in Relation to the Studied Groups

Table 3: MMSE I Domains According to the Type of CNS Infection

MMSE I	CNS infekcija			Kruskal Wallis Test (χ2)
	Gnojna	Serozna	Meningizam	p
Orientation in time and space	10,0(9,75-10,0)	10 (10-10)	10(10-10)	0,589
Attention	2,5 (1,75-3,0)	3,0 (3,0-3,0)	3,0 (3,0-3,0)	0,010
Calculus	3,0 (1,75-3,0)	4,0(2,75-5,0)	5,0 (3,75-5,0)	0,0001
Memory	1,0 (0,75-2,0)	3,0(1,0-3,0)	3,0 (2,0-3,0)	0,0001
Language	3,0 (2,0-3,0)	3,0 (3,0-3,0)	3,0 (3,0-3,0)	0,064
Ability to perform simple actions	6,0 (6,0-6,0)	6,0 (6,0-6,0)	6,0 (6,0-6,0)S	0,626

There is no statistically significant difference between the three examined categories in the part of MMSE I related to the domains: orientation in time and space during hospitalization p=0.989, language p=0.064 and the ability to perform simple actions p=0.626.

There is a statistically significant difference in the attention domain of MMSE I between the three examined categories p=0.010. The subjects with purulent CNS infection had on average significantly fewer points 2.5 (1.75-3.0) compared to the other two categories, p<0.05.

There is a statistically significant difference in the calculation domain of MMSE I between the three examined categories p=0.0001. The subjects with purulent CNS infection had on average significantly fewer points 3.0 (1.75-3.0) compared to the other two categories, p<0.05.

There is a statistically significant difference in the memory domain of MMSE I between the three examined categories p=0.0001. Subjects with purulent CNS infection had significantly fewer points, on average 1.0 (0.75-2.0), compared to the other two categories, p<0.05.

Table 4: MMSE II Domains According to the Type of CNS Infection

MMS II		CNS infection		Kruskal Wallis Test (χ2)
	Gnojna	Serozna	Meningizam	p
Orientation in time and space	10,0 (10,0-10,0)	10,0 (10,0-10,0)	10,0 (10,0-10,0)	0,115
Attention	3,0 (2,75-3,0)	3,0 (3,0-3,0)	3,0 (3,0-3,0)	0,582
Computing	3,0 (2,75-3,0)	5,0 (4,75-5,0)	5,0 (4,5-5,0)	0,001
Memory	2,0 (1,0-3,0)	3,0 (2,0-3,0)	3,0 (2,0-3,0)	0,064
Language	3,0 (3,0-3,0)	3,0 (3,0-3,0)	3,0 (3,0-3,0)	0,231
Ability to perform simple actions	6,0 (6,0-6,0)	6,0 (6,0-6,0)	6,0 (6,0-6,0)	0,368

There is no statistically significant difference between the three examined categories in the part of MMSE II related to orientation in time and space during hospitalization p=0.115, attention p=0.582, memory p=0.064, language p=0.231 and the ability to perform simple actions p=0.368.

There is a statistically significant difference in the calculation domain of MMSE II between the three examined categories p=0.001. Subjects with purulent CNS infection had on average significantly lower scores of 3.0 (2.75-3.0) compared to the other two categories, p<0.05.

Discussion

The average age for the three examined categories of this study is quite uniform, from 35.73±15.59 for viral infections, while 49.73±21.15 for purulent ones, so it is about the middle age. The age limit is comparable to other studies. A lower age limit is evident in researches that include the adult population and the children's group, which was excluded in this research [18].

The explanation of the prolonged time of illness until hospitalization for serous infections lies in the fact that the sample contained a significant proportion of the clinical diagnosis - meningitis, a diagnosis that represents a milder clinical form of the disease compared to encephalitis. The research we conducted did not differentiate meningitis, encephalitis or meningoencephalitis in relation to a viral or purulent type of infection, but the indirect assumption is that a significant proportion was viral meningitis, the clinical picture of which mimics other milder systemic viral infections, which is the reason for later reporting to the hospital. The study by Ahlbrecht et al. reported a sample with enterovirus CNS infection with a disease duration of up to 48 hours before hospitalization. Enteroviruses most often cause self-limiting acute meningitis, which is suspected late in the initial phase of the disease, only when the typical clinical picture of CNS infection develops [19].

Interestingly, CSF ferritin values are significantly elevated in purulent meningitis and in the pediatric population, despite the underdeveloped BBB, according to the study by Rezaei et al [20]. One of the objectives of this study was to monitor the nonspecific inflammatory marker ferritin in different entities of CNS infection. The CSF ferritin ratio is 8.30 ng/dL (5.30-20.43) for viral, while in bacterial it is 39.81 ng/dL (14.19-175.70). A significant difference is observed between the two entities, purulent and viral CNS infection, and although nonspecific, it can have great significance along with other diagnostic tools. The researchers, by analyzing different biomarkers, observed the nonspecific significance of the less frequently used, serum procalcitonin and CSF lactate [21].

Analyzing the short-term sequelae of the sample 6 months after discharge according to the MMSE test scale, a lower total value for purulent inflammation was found in both tests, the MMSE scale on the day of discharge and 6 months after discharge (MMSE I 24.0 / MMSE II 27.0), compared to the serous (MMS I 29.0 / MMS II 30.0) and the group with meningismus, which had the maximum number of points in both readings, therefore without changes in cognitive status. The authors who dealt with this issue also note that the prognosis of aseptic CNS infections, primarily meningitis as a diagnosis, is good. The explanation lies in the fact that in meningitis the brain parenchyma is not affected, and psychomotor structures remain intact. Such an analysis was made by Quist-Paulsen et al., following a one-year period of patients with aseptic meningitis and encephalitis, and found that 12 months after the discharge of patients with aseptic meningitis, no neuropsychological defects were detected, while the group of subjects with encephalitis had lower values on tests for the assessment of psychophysical skills. Learning and memory as an investigated category had lower scores in the category of encephalitis compared to meningitis in the category of serous infections [22].

Conclusion

A CSF ferritin value of 13.43 ng/dL can differentiate purulent CNS infection from meningism. Impairment of individual domains of cognition measured by MMSE I, such as "attention", "calculation" and "memory", is more pronounced in purulent CNS infections. Impairment of individual domain of MMSE II "calculation" is more pronounced in purulent CNS infection category.

References

1. Murthy SB, Moradiya Y, Shah J, Hanley DF, Ziai WC (2016) Incidence, predictors, and outcomes of ventriculostomy-associated infections in spontaneous intracerebral hemorrhage. Neurocrit Care 24: 389-396.
2. Parikh V, Tucci V, Galwankar S (2012) Infections of the nervous system. International journal of critical illness and injury science 2: 82.
3. Ludlow M, Kortekaas J, Herden C, Hoffmann B (2016) Neurotropic virus infections as the cause of immediate and delayed neuropathology. Acta Neuropathol 131: 159-184.
4. Klein RS, Garber C, Howard N (2017) Infectious immunity in the central nervous system and brain function. Nat Immunol 18: 132-141.
5. Barichello T, Generoso JS, Milioli G, Elias SG, Teixeira AL (2013) Pathophysiology of bacterial infection of the central nervous system and its putative role in the pathogenesis of behavioral changes. Revista brasileira de psiquiatria 35: 81-87.
6. Ranawaka UK (2015) The challenge of treating central nervous system infections. Ceylon Medical Journal 60: 155-158.
7. Dando SJ, Mackay-Sim A, Norton R, Currie BJ, John JA, et al. (2014) Pathogens penetrating the central nervous system: infection pathways and the cellular and molecular mechanisms of invasion. Clinical microbiology reviews 27: 691-726.
8. Giuleri SG, Chapuis-Taillard C, Manuel O (2015) Rapid detection of enterovirus in cerebrospinal fluid by a fully automated PCR assay is associated with improved management of aseptic meningitis in adult patients. J Clin Virol 62: 58-62.
9. Roos KL (2015) Bacterial Infections of the Central Nervous System. CONTINUUM: Lifelong Learning in Neurology 21: 1679–1691.
10. Ayton S, Faux NG, Bush AI (2015) Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes and are regulated by APOE. Nature Communications 6760: 6766.
11. Koperdanova M (2015) Interpreting raised serum ferritin levels. BMJ 351: h3692.
12. Kępa L, Oczko-Grzesik B, Stolarz W, Boroń-Kaczmarska A (2016) Cerebrospinal fluid ferritin concentration in patients with purulent, bacterial meningitis – own observations. Przegl Epidemiol 70: 593-603.
13. Benros ME, Sørensen HJ, Nielsen PR, Nordentoft M, Mortensen PB, et al. (2015) The association between infections and general cognitive ability in young men–a nationwide study. PLoS One 10: e0124005.
14. Hugo J, Ganguli M (2014) Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clinics in geriatric medicine 30: 421-42.
15. Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, et al. (2016) Mini-Mental State Examination for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database of Systematic Reviews 13: CD011145.
16. Tuijl JP, Scholte EM (2012) Screening for cognitive impairment in older general hospital patients: comparison of the six-item cognitive test with the Mini-Mental Status Examination. International journal of Geriatric Psychiatry 27: 755-762.
17. Albert SM (2014) MMSE 2.0: A new approach to an old measure. Neuroepidemiology 43: 26-27.
18. Abida FB, Abukhattaba M, Ghazouanie H, Khalila O, Gohara A, et al. (2018) Epidemiology and clinical outcomes of viral central nervous system infections. International Journal of Infectious Diseases 73: 85-90.
19. Ahlbrecht J, Hillebrand LK, Schwenkenbecher P, Ganzenmueller T, Heim A, (2018) et al. Cerebrospinal fluid features in adults with enteroviral nervous system infection. International Journal of Infectious Diseases 68: 94-101.
20. Rezaei M, Mamishi S, Mahmoudi S, Pourakbari B, Khotaei G, et al. (2013) Cerebrospinal fluid ferritin in children with viral and bacterial meningitis. Br J Biomed Sci 70: 101-103.
21. Polage CR, Cohenb SH (2016) State-of-the-Art Microbiologic Testing for Community-Acquired Meningitis and Encephalitis. Journal of Clinical Microbiology 54: 1197-1202.
22. Quist-Paulsen E, Ormaasen V, Kran AM, Dunlop O, Ueland PM, et al. (2019) Encephalitis and aseptic meningitis: short-term and long-term outcome, quality of life and neuropsychological functioning. Scientific Reports 9: 16158.