Tropical Journal of Pharmaceutical Research December 2021; 20 (12): 2625-2631
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i12.24

Original Research Article

Treatment effectiveness of zedoary turmeric oil on viral encephalitis in children, and its effect on serum and cerebrospinal levels of NSE and S100B

Zili Hou[1], Bing Han[2], Guosheng Xie[2], Cuilin Zhang[2], Fang Wang[2]*
[1]Department of Pharmacy, [2]Department of Paediatrics, Xingtai People's Hospital, Xingtai City 054001, Hebei Province, China

For correspondence: **Email: ff5p1b@163.com; **Tel:** +86 03193286439*

Sent for review: 10 July 2021 *Revised accepted: 26 November 2021*

Abstract

Purpose: *To investigate the effectiveness of the combination of zedoary turmeric oil, ganciclovir and interferon in the treatment of children with viral encephalitis, and its effect on neuron-specific enolase (NSE) and S100B.*
Methods: *One hundred (100) children with viral encephalitis were selected and assigned to control group (n = 50) and study group (n = 50). Children in control group received ganciclovir and interferon, while those in the study group received ganciclovir, interferon and zedoary turmeric oil. The treatment effectiveness, mitigation of symptoms, incidence of adverse reactions, and changes in levels of NSE and S100B in serum and cerebrospinal fluid (CSF) after treatment were analyzed for the two groups of children.*
Results: *Treatment effectiveness for the study group (98 %) was significantly higher than for the control group (84 %, $p < 0.05$). The time taken for the mitigation of clinical symptoms was markedly shorter in the study group than in control. There was a lower incidence of adverse reactions in children in the study group (2 %) than in controls (28 %). Serum NSE level (32.65 ± 13.18 ug/mL) and serum S100B level (5.56 ± 4.01 ug/mL) in the study group were significantly lower ($p < 0.05$) than the corresponding control levels (38.95 ± 11.95 ug/mL for NSE; and 8.18 ± 4.32 ug/ml for S100B).*
Conclusion: *The use of a combination of ganciclovir, interferon and zedoary turmeric oil treatment improves therapeutic effect in children with viral encephalitis. Therefore, the combination treatment merits clinical promotion and application.*

Keywords: *Zedoary turmeric oil, Viral encephalitis, NSE, S100B*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

High incidence of viral encephalitis occurs mostly in children in any season [1-3]. Since the severity of viral encephalitis varies in children, most children recover after treatment, but the conditions of some affected children deteriorate rapidly, often resulting in adverse sequelae, and even death [4-6]. Therefore, it is essential to diagnose and treat children with viral encephalitis as early as possible. Neuron-specific enolase (NSE) is one of the key enzymes involved in glycolysis. It is mainly found in neurons and neuroendocrine cells which release the enzyme

when brain cells undergo necrosis or degeneration. Therefore, the degree of nerve injury is reflected in level of NSE release. Moreover, S100B, a marker protein of neuroglia, is mainly distributed in central glial cells, and it is also an important indicator of sensitivity to brain injury.

The main treatment strategy for viral encephalitis involves the use of antiviral therapy with ganciclovir and interferon. Ganciclovir is a broad-spectrum drug used against DNA virus, and it has the advantages of easy passage through the blood-brain barrier, and increased blood drug concentration [7]. Interferon effectively inhibits viral replication. The combination of ganciclovir and interferon is often used in clinical treatment of viral encephalitis. The combined treatment is highly toxic, and it produces adverse reactions in children.

Zedoary turmeric oil has broad-spectrum resistance to DNA and RNA viruses, and it effectively improves the immune function of children [8]. At present, there is limited research on the treatment of pediatric viral encephalitis with zedoary turmeric oil based on ganciclovir and interferon in China. This study was aimed at investigating the clinical effectiveness of combination of zedoary turmeric oil, ganciclovir and interferon in the treatment of children with viral encephalitis, and its effect on NSE and S100B, so as provide a better option for the clinical treatment of viral encephalitis.

METHODS

General patient information

A total of 100 children with viral encephalitis who satisfied the inclusion criteria were randomly assigned to control and study (experimental) groups. The controls consisted of 28 males and 22 females aged 3 - 14 years (mean age = 6.78 ± 3.45 years), with disease course of 2 - 5 days (average course = 3.42 ± 0.45 days). The study group included 27 males and 23 females aged 3 - 14 years (mean age = 6.78 ± 3.45 years), with disease course of 2 - 6 days, and an average course of 3.75 ± 0.38 days. There were no marked differences between the control and study group children, with respect to age, gender, condition and number.

Inclusion criteria

Children in the following categories were included in the study: children who were clinically diagnosed with viral encephalitis, children with acute onset, and children with fever, consciousness disorder, vomiting and headache at different degrees.

This study received approval from the Ethics Committee of Xingtai People's Hospital (approval no. 20180555). The children and their families duly signed informed consent forms. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) [9].

Exclusion criteria

Children with other infectious diseases or other types of meningitis; children with brain trauma, children with severe kidney, heart and liver diseases, and those who were allergic to the treatments, were excluded.

Treatments

Following admission, both groups of children received basic treatments for maintaining acid-base balance, reducing fever, decreasing intracranial pressure, oxygen inhalation, protecting brain cells, sedation, and maintaining electrolyte balance.

Patients in control group received ganciclovir and interferon. For this purpose, ganciclovir (SFDA approval no. H20066700, specification: 0.25 g, manufacturer: Wuhan Changlian Laifu Pharmaceutical Limited Liability Company) was dissolved in 5 % glucose, and intravenously dripped into the children at a dose of 5 mg/kg for about 60 minutes, twice a day, with 14 consecutive days in all. Moreover, recombinant human interferon α-2b (SFDA approval number: S20040010, specification: 1 piece/3 million IU/box, manufacturer: Anhui Anke Biotech-nology) was intramuscularly injected into the children at a dose of 100,000 IU/kg, once a day for 14 consecutive days. The study group was treated with zedoary turmeric oil in the dose range of 10-15 mg/kg in glucose injection (SFDA approval number: H20043437, specification: 250 mL, manufacturer: Huiyinbi Group Jiangxi East Asia Pharmaceutical Co. Ltd.). The oil and glucose injection were intravenously dripped into the children, once a day, for 14 consecutive days.

Evaluation of clinical indices

Treatment effectiveness

If the clinical index was nil, and clinical symptoms completely disappeared in children, the treatment was considered as markedly effective. If the clinical index was mitigated, but clinical symptoms did not fully disappear, the treatment

was effective. However, if there were no changes in the clinical indices and symptoms, and if they tended to be aggravated in the children, the treatment was ineffective.

TTE = ME + E..... (1)

where *TTE* is total treatment effectiveness; *ME* is markedly effective, while *E* is effective.

Time taken for clinical improvement

The times taken for disappearance of clinical symptoms were determined and compared between the two groups. These included times taken for disappearance of convulsions, fever, consciousness disorder and headache.

Assessment of adverse reactions

The incidents of adverse reactions, i.e., leukopenia, thrombocytopenia and renal impairment were statistically compared between the two groups.

Assessment of levels of NSE and S100B

Before and after treatment, 5 mL of venous blood was collected from each patient in the two groups (on an empty stomach), and centrifuged for 30 min at 3000 rpm. The serum obtained was used to assay levels of NSE and S100B. Before and after treatment, 2 mL of cerebrospinal fluid was obtained *via* lumbar puncture from each patient in the two groups for the determination of the levels of NSE and S100B in cerebrospinal fluid using ELISA protein assay kits purchased from Shanghai Jining Shiye Co. Ltd, according to the kit instructions.

Statistical analysis

The data were statistically analyzed using the SPSS20.0 software. Measurement data are presented as mean ± SD, and they were compared using *t*-test. Counted data are presented as numbers and percentages [n (%)], and they were statistically analyzed with chi square (χ^2). Values of $p < 0.05$ indicated statistical significance

.

RESULTS

Treatment effectiveness

After treatment, the treatment effectiveness in children in the study group was significantly higher than that in the control group (Table 1, $p < 0.05$).

Table 1: Analysis of treatment effectiveness in two groups of children (n = 50)

Group	Markedly effective	Effective	Ineffective	Total effective-ness
Control	32	10	8	84 % (42/50)
Study	40	9	1	98 % (49/50)
χ^2				5.98
P-value				0.01

Time taken for mitigation of clinical symptoms

The times taken for reduction of clinical symptoms such as convulsion (2.47 ± 1.56 days), fever (3.28 ± 2.45 days), disorders in consciousness (2.75 ± 1.48 days) and headache (2.26 ± 1.22 days) post-treatment in the study group were significantly shorter than the corresponding times for convulsion (4.63 ± 2.23 days), fever (4.27 ± 2.89 days), disorders in consciousness (4.32 ± 2.58 days) and headache (5.79 ± 2.65 days) in the control group ($p < 0.001$). These results are shown in Figure 1.

As shown in Figure 1, the times taken for reduction of clinical symptoms in the study group were significantly shorter than those in the control group ($p < 0.001$).

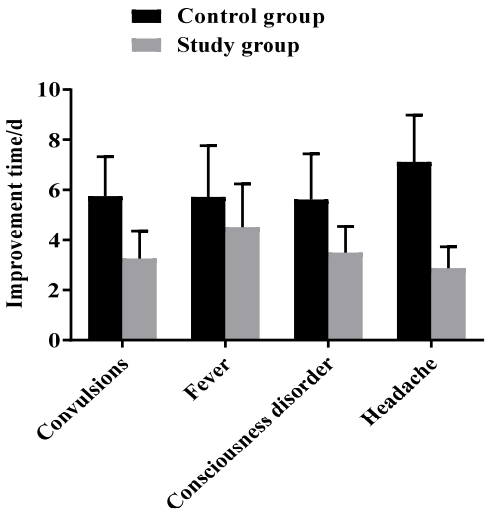

Figure 1: Time taken for reduction of clinical symptoms in two groups of children

Incidence of adverse reactions

There were markedly less adverse reaction incidents in the experimental group than in controls ($p < 0.001$), as shown in Table 2.

Table 2: Adverse reaction incidents in two groups of children (n = 50)

Group	Leukopenia	Thrombocytopenia	Renal impairment	Degree of adverse Reactions (%)
Control	7	7		28 (14/50)
Study	1	0	0	2（1/50）
X^2				13.25
***P*-value**				< 0.001

Analysis of changes in serum NSE levels

Before treatment, serum NSE levels were comparable between the study group (45.75 ± 19.55 ug/mL) and the control group (45.23 ± 19.38 ug/mL). After treatment, the serum NSE level of the study group (32.65 ± 13.18 ug/mL) was significantly lower than that of the control group (38.95 ± 11.95 ug/mL) ($p < 0.05$), as shown in Figure 2.

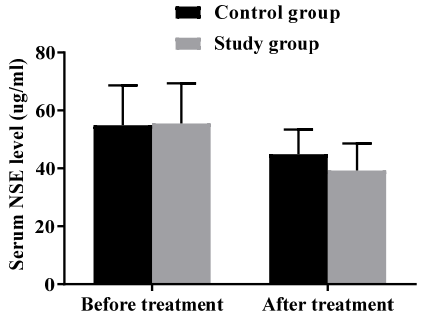

Figure 2: Serum NSE levels before and after treatment

As shown in Figure 2, the serum NSE was markedly lower in study group than in control group after treatment ($p < 0.05$).

Changes in serum S100B levels

Before treatment, serum S100B levels were comparable between the study group (10.09 ± 5.68 ug/mL) and the control group (10.02 ± 5.72 ug/mL). However, post-treatment serum S100B level of the study group (5.56 ± 4.01 ug/mL) was significantly lower than that of the control group (8.18 ± 4.32 ug/mL; $p < 0.001$), as shown in Figure 3. As shown in Figure 3, the serum S100B level was markedly lower in the study group than in the control group after treatment ($p < 0.001$).

Levels of NSE in cerebrospinal fluid (CSF)

Pre-treatment levels of CSF NSE were comparable between the study group (71.25 ± 28.45 ug/mL) and the control group (70.78 ± 27.87 ug/mL). However, post-treatment level of CSF NSE of the children was markedly decreased in the study group (32.98 ± 16.98 ug/mL), relative to that in the control group (42.71 ± 17.25 ug/mL; $p = 0.01$), as shown in Figure 4.

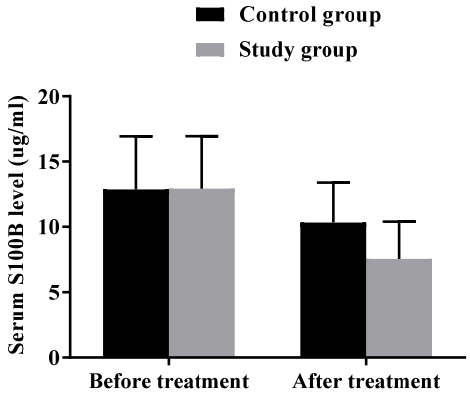

Figure 3: Serum S100B levels before and after treatment

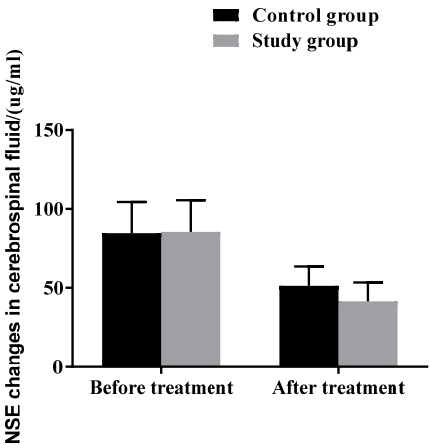

Figure 4: NSE levels in cerebrospinal fluid before and after treatment

S100B levels in cerebrospinal fluid (CSF)

Figure 5 shows that pre-treatment CSF S100B levels were comparable between the study group (19.45 ± 8.51 ug/mL) and the control group (19.45 ± 8.42 ug/mL). However, there was marked reduction in CSF S100B level of children in study group (7.43 ± 3.75 ug/mL), when compared to control group value (11.18 ± 6.38 ug/mL; $p < 0.001$).

DISCUSSION

Viral encephalitis is one of the infectious central nervous system diseases [10]. The pathogenesis of viral encephalitis is complex, but the causes

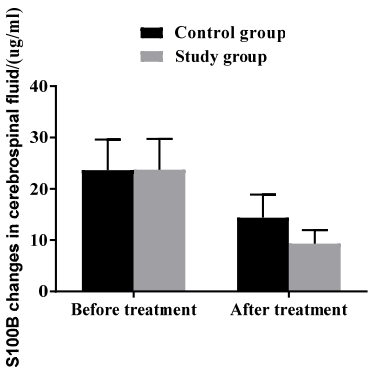

Figure 5: S100B levels in cerebrospinal fluid before and after treatment

are identifiable in only 25 % of cases [11]. At present, no specific drugs have been found for the treatment of viral encephalitis. Although some children may recover from the illness, children with herpes simplex virus encephalitis have poor prognosis. Therefore, antiviral treatment should be given to children once they are suspected of having viral encephalitis.

Currently, the preferred treatment for viral encephalitis is combination of ganciclovir and interferon [12,13]. Ganciclovir, an acyclic nucleoside analogue with broad-spectrum antiviral effects against DNA viruses, is converted to ganciclovir triphosphate by the virus due to induction of various cellular kinases, thereby inhibiting viral DNA synthesis and viral replication [14]. With small molecular weight, easy penetration into the blood-brain barrier, and the ability to achieve a blood concentration of more than 0.67 times of that in cerebrospinal fluid, ganciclovir is the preferred antiviral drug in the clinical treatment of viral encephalitis. Interferon is a bioactive glycoprotein that regulates the immune system [15]. Studies have revealed that as proteins, interferons block the translation process of host mRNA, and enhance specific cytotoxic effects of lymphocytes on target cells, with good clinical treatment effect on viral infectious diseases [16]. Although ganciclovir and interferon have good clinical effectiveness, they produce toxicity in children during the treatment process due to damage to the liver, kidney and other tissues. Therefore, it is essential to find an effective and low-toxicity clinical treatment for viral encephalitis in children.

Zedoary turmeric oil which is extracted from zedoary, is an antiviral drug which inhibits the replication of various RNA and DNA viruses in cells [17]. Zedoary turmeric oil and glucose injection effectively improve body immunity and inhibit viral proliferation. In addition, the oil exerts a positive effect by alleviating brain edema, relieving pain, promoting *qi* and *breaking stasis;* improving microcirculation, tranquilizing the mind and mitigating vascular injury. Zedoary turmeric oil and glucose injection are often applied in clinical practice due to the low side effects of the oil. However, its concentration should be reduced to less than 0.1 % when used as intravenous drip so as to effectively avoid stimulating the vessel wall, and to reduce allergies and vascular pain. There are no extant reports on the effect of combination of zedoary turmeric oil, ganciclovir and interferon in the treatment of pediatric viral encephalitis in China.

The present study was aimed at investigating the efficacy of combination of zedoary turmeric oil, ganciclovir and interferon in the treatment of children with viral encephalitis, and its effect on NSE and S100B. The results showed that treatment effectiveness, time taken for disappearance of clinical symptoms, and incidents of adverse reactions were significantly better in the experimental group than in controls. No renal impairment was found in the two groups of children. Adverse reactions in children in the control group disappeared after 1 week of drug withdrawal. This study has demonstrated that combined use of zedoary turmeric oil, ganciclovir and interferon effectively improved the clinical treatment effectiveness and quickly suppressed clinical symptoms in children with viral encephalitis, with marked decreases in adverse reactions.

Serum and cerebrospinal levels of NSE and S100B are the most commonly examined indicators in clinical studies of children with viral encephalitis. An acidic protein, S100B is mainly distributed in anterior pituitary cells and neuroglia cells, and it is metabolized and excreted by the kidney. It enters the cerebrospinal fluid when the brain is injured, leading to a rapid increase in S100B content in cerebrospinal fluid and its entrance into the peripheral blood. Therefore, there is a correlation between serum S100B level and CSF S100B level. It is known that NSE is an isoenzyme which plays an important role in glycolysis, and it is one of the specific markers of brain injury. It is mainly distributed in nerve cells and neurosecretory cells. Serum NSE level is lower than that in CSF. It has been reported that the levels of NSE and S100B in serum and cerebrospinal fluid are related to the severity of viral encephalitis in children [18]. In this study, post-treatment levels of NSE and S100B in serum and cerebrospinal fluid of the study group were significantly lower than those of the control group, indicating that combined use of zedoary turmeric oil, ganciclovir and interferon effectively

reduced NSE and S100B levels in serum and cerebrospinal fluid of children with viral encephalitis.

CONCLUSION

The combined use of ganciclovir, interferon and zedoary turmeric oil for the treatment of children with viral encephalitis improved therapeutic efficacy, reduced adverse reactions, and enhanced levels of NSE and S100B in serum and cerebrospinal fluid of the children. Thus, the combined treatment merits clinical promotion and application.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Zili Hou conceived and designed the study, and drafted the manuscript. Bing Han and Guosheng Xie collected, analyzed and interpreted the experimental data. Cuilin Zhang and Fang Wang revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

Open Access

REFERENCES

1. *Basaran S, Yavuz SS, Bali EA, Cagatay A, Oncul O, Ozsut H, Eraksoy H. Hyponatremia Is Predictive of HSV-1 Encephalitis among Patients with Viral Encephalitis. Tohoku J Exp Med 2019; 247(3): 189-195.*
2. *Johnson TP, Larman HB, Lee MH, Whitehead SS, Kowalak J, Toro C, Lau CC, Kim J, Johnson KR, Reoma LB, et al. Chronic Dengue Virus Panencephalitis in a Patient with Progressive Dementia with Extrapyramidal Features. Ann Neurol 2019; 86(5): 695-703.*
3. *Moniuszko-Malinowska A, Penza P, Czupryna P, Zajkowska O, Pancewicz S, Król M, Świerzbińska R, Dunaj J, Zajkowska J. Assessment of TLR-2 concentration in tick-borne encephalitis and neuroborreliosis. Scand J Clin Lab Invest 2019; 79(7): 502-506.*
4. *Zhang P, Lu K, Xia H. Multiple Factors Including Infections and Antibiotics Affecting New-Onset Epilepsy in Hemodialysis Patients. Ther Apher Dial 2019; 23(5): 404-408.*
5. *Moris P, Bauer KM, Currier JR, Friberg H, Eckels KH, Esquilin IO, Gibbons RV, Innis BL, Jarman RG, Simasathien S, et al. Cell-mediated immune responses to different formulations of a live-attenuated tetravalent dengue vaccine candidate in subjects living in dengue endemic and non-endemic regions. Hum Vaccin Immunother 2019; 15(9): 2090-2105.*
6. *Anesi JA, Silveira FP; AST Infectious Diseases Community of Practice. Arenaviruses and West Nile Virus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33(9): e13576.*
7. *Aneja J, Mahal P, Sudhakar G, Panda S, Tiwari S. Steroid-responsive Encephalopathy as a Semblance of Neuroleptic Malignant Syndrome in a Patient with Schizophrenia. Indian J Psychol Med 2019; 41(5): 487-491.*
8. *Pellett Madan R, Hand J; AST Infectious Diseases Community of Practice. Human herpesvirus 6, 7, and 8 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33(9): e13518.*
9. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
10. *El-Habashi N, El-Nahass ES, Abd-Ellatieff H, Saleh A, Abas O, Tsuchiya Y, Fukushi H, Yanai T. Lesions and Distribution of Viral Antigen in the Brain of Hamsters Infected With Equine Herpesvirus (EHV)-9, EHV-1 Strain Ab4p, and Zebra-Borne EHV-1. Vet Pathol 2019; 56(5): 691-702.*
11. *Basaran S, Yavuz SS, Bali EA, Cagatay A, Oncul O, Ozsut H, Eraksoy H. Hyponatremia Is Predictive of HSV-1 Encephalitis among Patients with Viral Encephalitis. Tohoku J Exp Med 2019; 247(3): 189-195.*
12. *Almeida MAB, Santos ED, Cardoso JDC, Noll CA, Lima MM, Silva FAE, Ferreira MS, Martins LC, Vasconcelos PFDC, Bicca-Marques JC. Detection of antibodies against Icoaraci, Ilhéus, and Saint Louis Encephalitis arboviruses during yellow fever monitoring surveillance in non-human primates (Alouatta caraya) in southern Brazil. J Med Primatol 2019; 48(4): 211-217.*

13. Yuan L, Zhang S, Liang S, Liu N, Yu X, Liang S. Deep brain stimulation of the anterior nucleus of the thalamus in a patient with super-refractory convulsive status epilepticus. Epileptic Disord 2019; 21(4): 379-384.
14. Li J, Gu Y, An H, Zhou Z, Zheng D, Wang Z, Wen Z, Shen HY, Wang Q, Wang H. Cerebrospinal fluid light and heavy neurofilament level increased in anti-N-methyl-d-aspartate receptor encephalitis. Brain Behav 2019; 9(8): e01354.
15. Thankachy S, Dash S, Sahu SS. Entomological factors in relation to the occurrence of Japanese encephalitis in Malkangiri district, Odisha State, India. Pathog Glob Health 2019; 113(5): 246-253.
16. Pantawane PB, Dhanze H, Ravi Kumar GVPPS, M R G, Dudhe NC, Bhilegaonkar KN. TaqMan real-time RT-PCR assay for detecting Japanese encephalitis virus in swine blood samples and mosquitoes. Anim Biotechnol 2019; 30(3): 267-272.
17. Mahapatra A, Dhal S, Bansal S, Turuk J, Choudhury S, Mishra P. Isolated Cerebellar Abscess by Burkholderia pseudomallei in an Immunocompromised Host: A Rare Case. Neurol India 2019; 67(4): 1149-1152.
18. Czupryna P, Grygorczuk S, Pancewicz S, Świerzbińska R, Zajkowska J, Krawczuk K, Dunaj J, Filipiuk J, Kruszewska E, Borawski K, et al. Evaluation of NSE and S100B in patients with tick-borne encephalitis. Brain Behav 2018; 8(12): e01160.