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HSV encephalitis: is the insight of the clinician still crucial for the outcome?

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Abstract: Herpes simplex virus (HSV) encephalitis is an acute infection of the Central Nervous System (CNS). During the last two decades its incidence has a ten-fold increase, while mortality rate exceeds 70%, if left undiagnosed and thus untreated. Clinical manifestations, imaging studies, cerebrospinal fluid (CSF) analysis and electroencephalogram (EEG) are the basis of diagnostic approach. Even when CSF analysis seems normal, imaging studies are not specific and HSV polymerase chain reaction (PCR) test is negative, the clinician should be more aggressive, if clinical presentation is indicative for HSV encephalitis, by administrating acyclovir early after patient's admission. The aim of this short review article, after systematic research of the relevant up to date literature, is to emphasize the insight of the clinician as for the early diagnosis and the prompt therapeutic intervention, which are crucial for the outcome and vital for the affected patient.

Key words: HSV, encephalitis, early diagnosis, PCR test, MRI, acyclovir.

Introduction

HSV encephalitis is an acute CNS infectious disease, involving the limbic structures, the median temporal cortex and the orbitofrontal regions. Annual incidence of HSV encephalitis ranges from 1/500,000/ year to 1.2/100,000/year and has increased ten-

fold during the last two decades [1–3]. Mortality rate of encephalitis in England is estimated up to 7%. HSV encephalitis leads to death in more than 70% of all cases if left untreated or administration of acyclovir is significantly delayed [4]. More than 95% of untreated survivors will face life-long neurological deficits [5]. In another recent retrospective study by Sili, mortality rate was 8%, while 69% of survivors recovered with recovered with complications [6].

Up to 70% of all cases of viral encephalitis are of unknown cause, while, according to other authors, this percentage may reach up to 85% [4, 7]. However, in a large multicenter prospective study by the above authors, it was documented that the cause of encephalitis was infectious in 42% of all patients. Among them, HSV was the main pathogen (19% of all patients), followed by Varicella-zoster virus (VZV) (5%) and Mycobacterium tuberculosis (5%). In 37% of all cases the cause remained unknown [8]. Based upon clinical manifestation, HSV encephalitis is not distinguished from other viral causes of encephalitis [9].

HSV-1 is responsible for almost 90% of all cases of HSV encephalitis during adulthood. On the other hand, HSV-2 is involved in neonatal meningoencephalitis, congenitally acquired, due to mother to infant transmission of HSV-2 of genitalia during delivery process [10]. Primary infection occurs in 30% of all cases, while the rest cases are due to reactivation. The first is most frequent in neonates, while HSV encephalitis in adults occurs usually after re-activation [11].

It remains unclear how HSV gains access to CNS in humans. Retrograde transport through the olfactory or trigeminal nerves, or hematogenous dissemination constitutes the suggested routes [12]. Pathogenetic mechanisms of CNS infection include: a) reactivation of latent HSV in the trigeminal neurons and spread to brain, b) primary infection and c) viral reactivation of a latent HSV infection in the brain itself [10]. One third of all cases are due to primary infection, while the rest occurs after re-activation of a latent HSV infection or re-infection by a second HSV [13]. HSV-1 is capable of producing a life-long infection in the neurons of trigeminal ganglia, while interferon type 1 and autophagy play a significant role in neuronal antiviral response [14]. Except for the role of interferons in the innate immune response, proinflammatory cytokine response is also associated with clinical severity and brain damage, posing the question for the use of IL-1 antagonists in the therapeutic approach of patients with HSV encephalitis [15]. Defective TLR3 expression is associated with increased neuroinvasion of HSV, suppression of innate immune response and enhanced viral replication. Mutation of TLR3 and TLR3 pathway genes lead to decreased production of IFN type I by the microglia, and thus to predisposition to HSV neuroinvasion [16, 17].

Clinical presentation

Typical signs and symptoms of HSV encephalitis include: fever, consciousness disturbances, disorientation, behavioral disorders, language disorders, seizures or status epilepticus and focal neurologic deficit [18]. Fever, headache, motor deficit and seizure are considered as key points in clinical presentation [19].The amorphous character of the symptoms at the onset of the disease can be easily misinterpreted by the clinician [20].

In a recent multinational study focused on herpetic encephalitis, the most frequent clinical manifestations were: changes in consciousness (80.2%), disorientation (58.3%), personality changes (32.4%), speech disorders (28.8%), convulsion (25.9%), amnesia (25.9%), hallucinations (6.1%) and abulia (4.2%), while hemiparesis and cranial nerve palsies were relatively rare (<1% for both). Regarding clinical signs, fever is the most common (83.4%), headache follows (59.9%), while neck stiffness, Kernig and Brudzinski signs are less frequent [21]. Clinical manifestations such as aphasia, personality changes and mutism are associated with frontotemporal involvement [22]. Frontal and temporal lobe involvement are also conjugated with abnormal behavior, psychosis, confusion and disorientation seen in those patients [23, 24]. Olfactory hallucinations represent temporal lobe seizures [25].

Incidence of seizures during the acute phase of encephalitis is 7–67%, while they constitute a poor prognostic factor, associated with almost 30% mortality rate [26]. CNS infections are accompanied with seizures in one third of all patients, which are asymptomatic in 50% of that group and are recognized in continuous EEG [27].

Diagnostic approach

Clinical manifestations, imaging modalities, lumbar puncture (LP) and CSF analysis, and EEG are the major steps towards diagnosis.

An urgent CT brain scan should be conducted first in suspected cases, prior to LP, when one or more of the following exist: evidence of obstructive raised intracranial pressure, GCS<13, fall in GCS>2, focal neurological signs, abnormal posturing, papilloedema and immunocompromised [28].

Regarding CSF analysis, usual findings are: mononuclear cell pleocytosis (at least 40 WBC/mm3, average 100–200 WBC/mm^3) and mild elevation of protein levels (median: 70–100 mg/dl) [23].

Normal initial CSF analysis should not be evaluated in high suspicion of encephalitis and acyclovir administration should not be delayed. A new lumbar puncture in 4th day is indicated [29].

HSV CSF PCR test is the reference method for the diagnosis of HSV encephalitis, a test with 98% specificity and 94% sensitivity [3]. It is not rare that PCR turns out

negative, early after the onset of symptomatology, while it usually remains positive for seven days after administration of acyclovir [30]. Repeat of HSV PCR after initiation of acyclovir therapy is also indicated. A negative HSV PCR at the end of the treatment constitutes a good prognostic factor [29]. CSF sampling earlier than the first 3 days or later than 2 weeks after the onset of symptoms can reduce the possibility of a positive PCR result [31].

According to the study by Ziyaeyan *et al.* regarding to HSV PCR testing in CSF samples of 236 patients with suspected herpetic encephalitis, the authors document that: a) the greater the viral load early after the onset of the disease, the longer the PCR test remains positive, b) if CSF samples are collected early, PCR testing may be negative, c) in cases of a negative PCR test, the clinician should repeat the test after two days and d) if acyclovir is administered for one week or less, then PCR test remains positive [32].

In the study performed by Saraya *et al.*, 6/23 patients (26.1%) with confirmed HSV encephalitis had normal WBC in collected CSF samples. Viral load in the pleocytosis group was higher than that in the normocellular group, with no detected correlation between the viral load and the prognosis. Four out of those six patients had no specific findings in the MRI brain scan. Thus, authors suggest that, even when CSF is normocellular and MRI is not specific, HSV encephalitis cannot be excluded, and in high clinical suspicion, HSV PCR test should be immediately ordered [23].

Formsgaard *et al.* concluded that evaluation of intrathecal synthesis of HSV specific IgG antibodies in the CSF, in combination with HSV PCR test improves sensitivity of HSV detection in suspected cases [33]. IgG detection assays usually turn out positive during the second week after the onset of the disease (>10 days) and remain positive for a long period of time. This time dependent assay should be performed on the second week of disease's course, after two negative PCR tests on 1st and 4th day, enhancing the possibility of HSV detection [34].

At the end of acyclovir treatment, a new CSF specimen should be obtained for PCR test. A negative test constitutes a good predictor, while a positive for HSV-1 test is an indicator for continuation of antiviral treatment [35].

Main radiologic features are: a) hypodense lesions of temporal lobes and orbitofrontal regions, sometimes with petechial hemorrhage on brain CT scanning and b) hypointensity in T1 and hyperintensity in T2 images on brain MRI scanning. Rarely, viral encephalitis cannot be distinguished from neoplastic lesions and MR spectroscopy may not be helpful in differential diagnosis. In those cases, when presence of neoplastic lesion cannot be excluded, brain tissue biopsy may be required before lumbar puncture and CSF analysis, a process that would precipitate central herniation [36].

Although brain CT scan is in most cases the first imaging modality to be performed in suspected cases of acute encephalitis, prior to lumbar puncture (exclusion of

a brain lesion with mass effect), it is significantly inferior to MRI scan, regarding diagnosis of acute infectious encephalitis. The latter may implicate the causative agent of encephalitis, based upon the imaging pattern, while it is usually crucial for differential diagnosis [37]. Despite its role on the acute phase, MRI imaging may also provide a criterion of responsiveness to the applied treatment, by the use of specific techniques [38]. Overall, sensitivity of imaging in cases of HSV encephalitis is almost 80% for both CT and MRI, however, specificity of MRI within the first 10 days after the onset of clinical manifestations reaches up to 100% for the same pathology [39].

Differential diagnosis

Other causative infectious agents of encephalitis that should be included in differential diagnosis include: Varicella-zoster virus (VZV), Mycobacterium tuberculosis, Listeria monocytogenes, European tick-borne encephalitis virus (TBEV) and Mycoplasma pneumoniae. An emerging cause of acute encephalitis in Greece is West Nile virus (WNV). Other pathogens should be excluded based upon the meticulous interpretation of epidemiological data in each region [10, 40, 41]. Bacterial and fungal abscesses must also be included in differential diagnosis [42].

Mesial temporal sclerosis, gliomatosis cerebri and mitochondrial encephalomyopathy (MELAS) should also be excluded especially when bilateral temporal lobe involvement is detected on MRI scan [42]. The following must be excluded, as well: acute disseminated encephalomyelitis (ADEM), paraneoplastic limbic encephalopathy, Hurst's disease, systemic lupus erythematosus (SLE), primary CNS lymphoma, complex partial status epilepticus and neurosyphilis [43]. Autoimmune central nervous vasculitis and cerebral amyloid angiopathy related inflammation should also be included [44].

Therapeutic strategy

Main results of the retrospective study conducted by Sheybani *et al.* were that: a) 18% of all patients with viral encephalitis had a normal CSF analysis, b) brain CT scanning was abnormal only in 50% of the study group c) brain MRI was suggestive of encephalitis in the vast majority of the patients — 92% and d) CSF HSV-1 PCR test was negative in 24% of all patients. It is thus concluded that high clinical suspicion is required, as HSV-1 encephalitis cannot be excluded, even when CSF analysis and imaging studies are not suggestive of the diagnosis. In cases of febrile encephalopathy of unknown origin, the early administration of acyclovir may be crucial for the patient's survival [45].

According to the study conducted by Poisy *et al.*, chronic alcohol abuse, high Knaus score and delay in the first brain CT or MRI scan were the factors associated

independently with delay in administration of acyclovir (p = 0.02, 0.007 and <0.001 respectively). White cell count <10/mm^3 in CSF increased 2.5 fold the risk of late administration of acyclovir, finding not statistically significant (p = 0.17). As late initiation of acyclovir is the most significant modifiable prognostic factor in HSV encephalitis, authors suggest that when the clinician confronts a patient with severe underlying disease or chronic alcohol abuse, in high suspicion for HSV encephalitis, even when CSF appears normal, early initiation of acyclovir is crucial for the final outcome [46].

In a more recent study by Poisy *et al.*, higher Knaus score (p = 0.08), delay in acyclovir treatment (p = 0.006), older age (p = 0.04) and presence of red blood cells in the CSF (p = 0.05) were associated with higher morbidity and mortality. However, the authors did not document a correlation between the HSV viral load in the CSF and the prognosis. They suggest that abnormal immunological response of the host and not intense viral replication determine the severity of the disease, as interpreted by correlation with viral load and red blood cells count [47].

Wang and Liu consider MRI imaging of higher sensitivity for the diagnosis, compared with HSV PCR test, which is considered as the gold standard method for the confirmation of the diagnosis. Based on the fact that HSV PCR test may be negative early after the onset of the symptoms, the authors suggest the prompt performance of MRI and early administration of acyclovir, in highly suspected cases. They conclude that sole reliance on PCR test may be dangerous, leading to poor outcome, if the patient is left untreated [48]. Temporal lobe edema or hemorrhage is a pathognomonic for HSV encephalitis MRI pattern [49]. The importance of MRI imaging in HSV encephalitis is highlighted by the findings of Sili *et al.* in their retrospective study, in which duration of disease before hospital admission (odds ratio (OR) = 1.24) and the extent of brain involvement on MRI at the time of admission were the two independent risk factors associated with poor outcome [6].

Clinical manifestations, imaging studies, CSF analysis and EEG are the basis of diagnostic approach in encephalitis. Those patients presenting with at least two seizures or status epilepticus, severe organ damage or behavior alteration usually require temporary hospitalization in ICU. GCS<8 or status epilepticus are absolute indications for intubation [29]. Male gender, third age, lower GCS score and delay in initiation of acyclovir >2 days after the onset of the symptoms are the main predictors of unfavorable outcome. High suspicion of the clinician, rapid diagnosis and prompt administration of acyclovir are the triptych of success in possible or confirmed cases of HSV encephalitis [50]. In cases of high suspicion for HSV encephalitis, prompt intravenous administration of acyclovir (10 mg/kg every 8 hours) is the treatment of choice. Duration of the treatment usually ranges from 14 to 21 days [35]. The role of corticosteroids in HSV encephalitis is ambiguous, although they are usually administered in clinical practice [29]. IL-1 antagonists may offer as adjunctive

treatment in infectious encephalitis, although well designed randomized controlled trials should be conducted to establish them as second line agents [15].

Conclusion

Even when CSF analysis seems normal, imaging studies are not specific and HSV PCR test is negative, the clinician should be more aggressive, if clinical presentation is indicative for HSV encephalitis, by administrating acyclovir early after patient's admission. Thus, medical history, physical examination and high clinical suspicion cannot be replaced, in the context of early diagnosis and prompt therapeutic intervention.

Conflict of interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

References

1. *Jouan Y., Grammatico-Guillon L., Espitalier F., Cazals X., Francois P., Guillon A.*: Long-term outcome of severe herpes simplex encephalitis: a population-based observational study. Crit Care. 2015; 15: 1–9.
2. *George B.P., Schneider E.B., Venkatesan A.*: Encephalitis hospitalization rates and inpatient mortality in the United States, 2000–2010. PLoS One. 2014; 9 (9): e104169.
3. *Whitley R.J.*: Herpes simplex encephalitis: adolescents and adults. Antiviral Res. 2006; 71: 141–148.
4. *Granerod J., Crowcroft N.S.*: The epidemiology of acute encephalitis Neuropsychol. Rehabil. 2007, 17: 406–428.
5. *Kennedy P.G., Steiner I.*: Recent issues in herpes simplex encephalitis. J. Neurovirol. 2013, 19: 346–350.
6. *Sili U., Kaya A., Mert A.*: HSV encephalitis study group, Herpes simplex virus encephalitis: clinical manifestations, diagnosis and outcome in 106 adult patients. J Clin Virol. 2014 Jun; 60 (2): 112–118.
7. *Steiner I., Budka H., Chaudhuri A., et al.*: Viral encephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2005; 12: 331–343.
8. *Granerod J., Ambrose H., Davies N., et al.*: Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010; 10: 835–844.
9. *Croll B., Dillon Z., Weaver K., Greenberg M.*: MRI diagnosis of herpes simplex encephalitis in an elderly man with non specific symptoms. Radiology Case Reports. 2017; 12 (1): 159–160.
10. *Silva M.T.T.*: Viral encephalitis. Arq Neuropsiquiatr. 2013; 71: 703–709.
11. *Shives K.D., Tyler K.L., Beckham J.D.*: Molecular mechanisms of neuroinflammation and injury during acute viral encephalitis, J Neuroimmunol. 2017 Jul; 308: 102–111.
12. *Bradshaw M.J., Venkatesan A.*: Herpes Simplex Virus-1 Encephalitis in Adults: Pathophysiology, Diagnosis, and Management, Neurotherapeutics. 2016 Jul; 13 (3): 493–508.

13. *Whitley R.J., Gnann J.*: Viral encephalitis: familiar infections and emerging pathogens. Lancet. 2002; 359: 507–514.
14. *Katzenell S., Leib D.A.*: Herpes Simplex Virus and Interferon Signaling Induce Novel Autophagic Clusters in Sensory Neurons. J Virol. 2016 Apr; 90 (9): 4706–4719.
15. *Michael B.D., Griffiths M.J., Granerod J., et al.*: The Interleukin-1 Balance During Encephalitis Is Associated With Clinical Severity, Blood-Brain Barrier Permeability, Neuroimaging Changes, and Disease Outcome, J Infect Dis. 2016 May; 213 (10): 1651–1660.
16. *Li J., Ye L., Wang X., et al.*: Induction of interferon-γ contributes to toll-like receptor 3-mediated herpes simplex virus type 1 inhibition in astrocytes. J Neurosci Res. 2012, 90: 399–406.
17. *Reinert L.S., Lopušná K., Winther H., et al.*: Sensing of HSV-1 by the cGAS-STING pathway in microglia orchestrates antiviral defence in the CNS, Nat Commun. 2016 Nov; 7: 13348.
18. *Fillatre P., Crabol Y., Morand P., et al.*: Infectious encephalitis: Management without etiological diagnosis 48 hours after onset. Med Mal Infect. 2017; 47 (3): 236–251.
19. *Tyler K.L.*: Update on herpes simplex encephalitis. Rev Neurol Dis. 2004; 1: 169–178.
20. *Cooper J., Kierans C., Defres S., Easton A., Kneen R., Solomon T.*: Diagnostic Pathways as Social and Participatory Practices: The Case of Herpes Simplex Encephalitis. PLoS ONE. 2016; 11 (3): e0151145. doi: 10.1371/journal.pone.0151145.
21. *Cag Y., Erdem H., Leib S., et al.*: Managing atypical and typical herpetic central nervous system infections: results of a multinational study. Clin Microbiol Infect. 2016; 22 (6): 568.e9-568.e17.
22. *Raschilas F., Wolff M., Delatour F., Chaffaut C., De Broucker T., Chevret S., et al.*: Outcome and prognostic factors for Herpes Simplex Encephalitis in adult patients: Results of a multi-centre study. Clin Infec Dis. 2002; 35: 254–260.
23. *Saraya A., Wacharapluesadee S., Petcharat S., et al.*: Normocellular CSF in herpes simplex encephalitis. BMC Res Notes. 2016, 9: 95. doi: 10.1186/s13104-016-1922-9.
24. *Tuzun E., Dalmau J.*: Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist. 2007; 13: 261–271.
25. *Johnson R.T.*: Acute encephalitis. Clin Infect Dis. 1996 Aug; 23 (2): 219–224.
26. *Misra U.K., Tan C.T., Kalita J.*: Viral encephalitis and epilepsy. Epilepsia. 2008; 49 (Suppl. 6): 13–18.
27. *Carrera E., Claassen J., Oddo M., Emerson R.G., Mayer S.A., Hirsch L.J.*: Continuous electroencephalographic monitoring in critically ill patients with central nervous system infections. Arch Neurol. 2008; 65: 1612–1618.
28. *Solomon T., Michael B., Smith P., et al.*: Management of suspected viral encephalitis in adults — Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012; 64: 347–373.
29. *Goulenok R., Buzelé R., Duval X., et al.*: Management of adult infectious encephalitis in metropolitan France. Med Mal Infect. 2017 May; 47 (3): 206–220.
30. *Sabah M., Mulcahy J., Zeman A.*: Herpes simplex encephalitis. BMJ. 2012; 344: e3166.
31. *Davies N., Brown L., Gonde J., et al.*: Factors influencing PCR detection of viruses in cerebrospinal fluid of patients with suspected CNS infections. J Neurol Neurosurg. Psychiatry. 2005; 76: 82–87.
32. *Ziyaeyan M., Alborzi A., Borhani Haghighi A., Jamalidoust M., Moeini M., Pourabbas B.*: Diagnosis and quantitative detection of HSV DNA in samples from patients with suspected herpes simplex encephalitis. Braz J Infect Dis. 2011; 15: 211–214.
33. *Fomsgaard A., Kirkby N., Jensen I., Vestergaard B.*: Routine diagnosis of herpes simplex virus (HSV) encephalitis by an internal DNA controlled HSV PCR and an IgG-capture assay for intrathecal synthesis of HSV antibodies. Clinical and Diagnostic Virology. 1998, 9 (1): 45–56.
34. *Denes E., Labach C., Durox H., et al.*: Intrathecal synthesis of specific antibodies as a marker of herpes simplex encephalitis in patients with negative PCR. Swiss Med Wkly. 2010; 140: w13107.
35. *Tunkel A.R., Glasser C.A., Bloch K.C., et al.*: The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008; 47: 303–327.

36. *Peeraully T., Landolfi J.*: Herpes Encephalitis Masquerading as Tumor. ISRN Neurology Volume 2011, Article ID 474672, 4 pages.
37. *Bertrand A., Leclercq D., Martinez-Almoyna L., Girard N., Stahl J.P., De-Broucker T.*: MR imaging of adult acute infectious encephalitis. Med Mal Infect. 2017 May; 47 (3): 195–205.
38. *Defres S., Keller S.S., Das K., et al.*: A Feasibility Study of Quantifying Longitudinal Brain Changes in Herpes Simplex Virus (HSV) Encephalitis Using Magnetic Resonance Imaging (MRI) and Stereology. PLoS One. 2017; 12 (1): e0170215.
39. *Granerod J., Davies N.W., Mukonoweshuro W., et al.*: Neuroimaging in encephalitis: analysis of imaging findings and interobserver agreement. Clin Radiol. 2016; 71 (10): 1050–1058.
40. *Danis K., Papa A., Theocharopoulos G., et al.*: Outbreak of West Nile virus infection in Greece, 2010. Emerging Infectious Diseases. 2011; 17 (10): 1868–1872.
41. *Boucher A., Herrmann J.L., Morand P., et al.*: Epidemiology of infectious encephalitis causes in 2016. Med Mal Infect. 2017 May; 47 (3): 221–235.
42. *Chow F., Glaser C., Sheriff H., et al.*: Use of Clinical and Neuroimaging Characteristics to Distinguish Temporal Lobe Herpes Simplex Encephalitis From Its Mimics, Clinical Infectious Diseases. 2015; 60 (9): 1377–1383.
43. *Vedes E., Geraldo A., Rodrigues R., Reimao S., Ribeiro A., Antunes F.*: Neurosyphilis versus Herpes Encephalitis in a Patient with Confusion, Memory Loss, and T2-Weighted Mesiotemporal Hyperintensity. Case Reports in Infectious Diseases. 2012, Article ID 154863, 3 pp.
44. *Buerger K., Zerr K., Salazar R.*: An unusual presentation of herpes simplex encephalitis with negative PCR. BMJ Case Rep. 2015. doi: 10.1136/bcr-2015-210522.
45. *Sheybani F., Arabikhan H.R., Naderi H.R.*: Herpes Simplex Encephalitis (HSE) and its outcome in the Patients who were Admitted to a Tertiary Care Hospital in Mashhad, Iran, over a 10-year Period. J Clin Diagn Res. 2013; 7 (8): 1626–1628.
46. *Poisy J., Wolff M., Dewilde A., et al.*: Factors associated with delay to acyclovir administration in 184 patients with herpes simplex virus encephalitis. Clin Microbiol Infect. 2009; 15: 560–564.
47. *Poisy J., Champenois K., Dewilde A., et al.*: Impact of Herpes simplex virus load and red blood cells in cerebrospinal fluid upon herpes simplex meningo-encephalitis outcome. BMC Infectious Diseases 2012; 12: 356.
48. *Wang W.-S., Liu C.-P.*: The Clinical Presentation, Diagnosis, Treatment, and Outcome of Encephalitis: Five Years of Experience at a Medical Center in Northern Taiwan. International Journal of Gerontology. 2011; 5: 9–12.
49. *Maschke M., Kastrup O., Forsting M., Diener H.C.*: Update of neuroimaging in infectious central nervous system disease. Curr Opin Neurol. 2004; 17: 475–480.
50. *Erdem H., Cag Y., Ozturk-Engin D., et al.*: Results of a Multinational Study Suggest the Need for Rapid Diagnosis and Early Antiviral Treatment at the Onset of Herpetic Meningoencephalitis. Antimicrob Agents Chemother. 2015; 59 (6): 3084–3089.