OPEN ACCESS

Middle East Research Journal of Medical Sciences
ISSN: 2789-7699 (Print) & ISSN: 2958-2024 (Online)
Frequency: Bi-Monthly
DOI: https://doi.org/10.36348/merjms.2024.v04i04.004

KUWAIT SCHOLARS PUBLISHER
Website: http://www.kspublisher.com/
Email: office@kspublisher.com

Evaluation of the Efficiency of Neural Enolase (NSA) in the Diagnosis of Viral Encephalitis: A Medical Review

Carlos Henrique Marchiori[1*], Marco Vinícios de Oliveira Santana[1], Klebert de Paula Malheiros[1]
[1]Teachers and Researchers of the Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil

Abstract: Encephalitis is an inflammation that occurs in the brain when a virus in some cases, bacteria attack it directly, and can also be triggered by other factors. It is an inflammatory process of the meninges, the membranes that cover the central nervous system. Enolase isoenzyme found in neuronal and neuroendocrine tissues. Its levels in tissues other than erythrocytes are negligible. Its measurement is useful for monitoring tumors of neuroendocrine origin, such as neuroblastoma, pheochromocytoma, medullary thyroid carcinoma, small cell lung carcinoma, melanoma, and some pancreatic tumors. NSE concentrations in cerebrospinal fluid (CSF) are often elevated in diseases that result in relatively rapid neuronal destruction. This review aims to evaluate the efficiency of neural enolase (NSA) in diagnosing viral encephalitis. The methodology used an integrative literature review and a synthesis process to develop the study, expand the understanding of knowledge, and achieve the expected results. The integrative literature review is a method that aims to synthesize results obtained in research on a topic or issue, in a systematic, ordered, and comprehensive way. It is called integrative because it provides broader information on a subject/problem, thus constituting a body of knowledge. To carry out the study, a search for scientific articles was carried out through the Virtual Health Library, in the SCIELO, LILACS, and PUBMED databases, using the terminologies registered in the Health Sciences descriptors, encephalitis, enolase, virus, and diagnosis.

Keywords: Brain, Diseases, Encephalon, Inflammation, Nervous System.

Review Paper

***Corresponding Author:**
Carlos Henrique Marchiori
Teachers and Researchers of the Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil

How to cite this paper:
Carlos Henrique Marchiori *et al* (2024). Evaluation of the Efficiency of Neural Enolase (NSA) in the Diagnosis of Viral Encephalitis: A Medical Review. *Middle East Res J. Med. Sci, 4*(4): 86-99.

Article History:
| Submit: 07.07.2024 |
| Accepted: 06.08.2024 |
| Published: 09.08.2024 |

1. INTRODUCTION

1.1. Encephalopathy

The name is given to diseases that affect the brain, causing disorders of perfusion, metabolism, and neurotransmission. Among the encephalopathies, the most prominent are hypertensive, hypoxic-ischemic, metabolic, uremic, traumatic, Wernicke-Korsakoff, toxic, and hepatic encephalopathy (ABCMED, 2017; Tholey, 2023; Gross, 2024; Shutterstock, 2024).

Hepatic encephalopathy is the deterioration of brain function that occurs in people with severe liver disease because toxic substances normally eliminated by the liver accumulate in the blood and reach the brain. Hepatic encephalopathy occurs in people with chronic, prolonged liver disease (Figure 1) (ABCMED, 2017; Le *et al*., 2020; Tholey, 2023; Shutterstock, 2024).

This intoxication can be acute or massive. The initial symptoms of chronic traumatic encephalopathy typically include more or less the following: Mood disturbance: Depression, irritability and/or hopelessness. Behavioral abnormalities: Impulsivity, explosiveness, and/or aggression. Cognitive impairment: Memory loss, executive dysfunction, and/or dementia (ABCMED, 2017; Tholey, 2023; Gross, 2024; Shutterstock, 2024).

1.2. Encephalitis

Is an inflammation that occurs in the brain when a virus in some cases, bacteria attack it directly, and can also be triggered by other factors. It is an inflammatory process of the meninges, the membranes that cover the central nervous system. In some cases, encephalitis can result from an immune system disorder. Mild cases may cause no symptoms or may present with mild flu-like symptoms. Severe cases can be fatal. Immediate medical attention is needed for symptoms such as confusion, hallucinations, seizures, weakness, and loss of sensation (Figure 2) (Bale, 2015; Gol *et al.*, 2015; Bohmwald *et al.*, 2021; Greenlee, 2024).

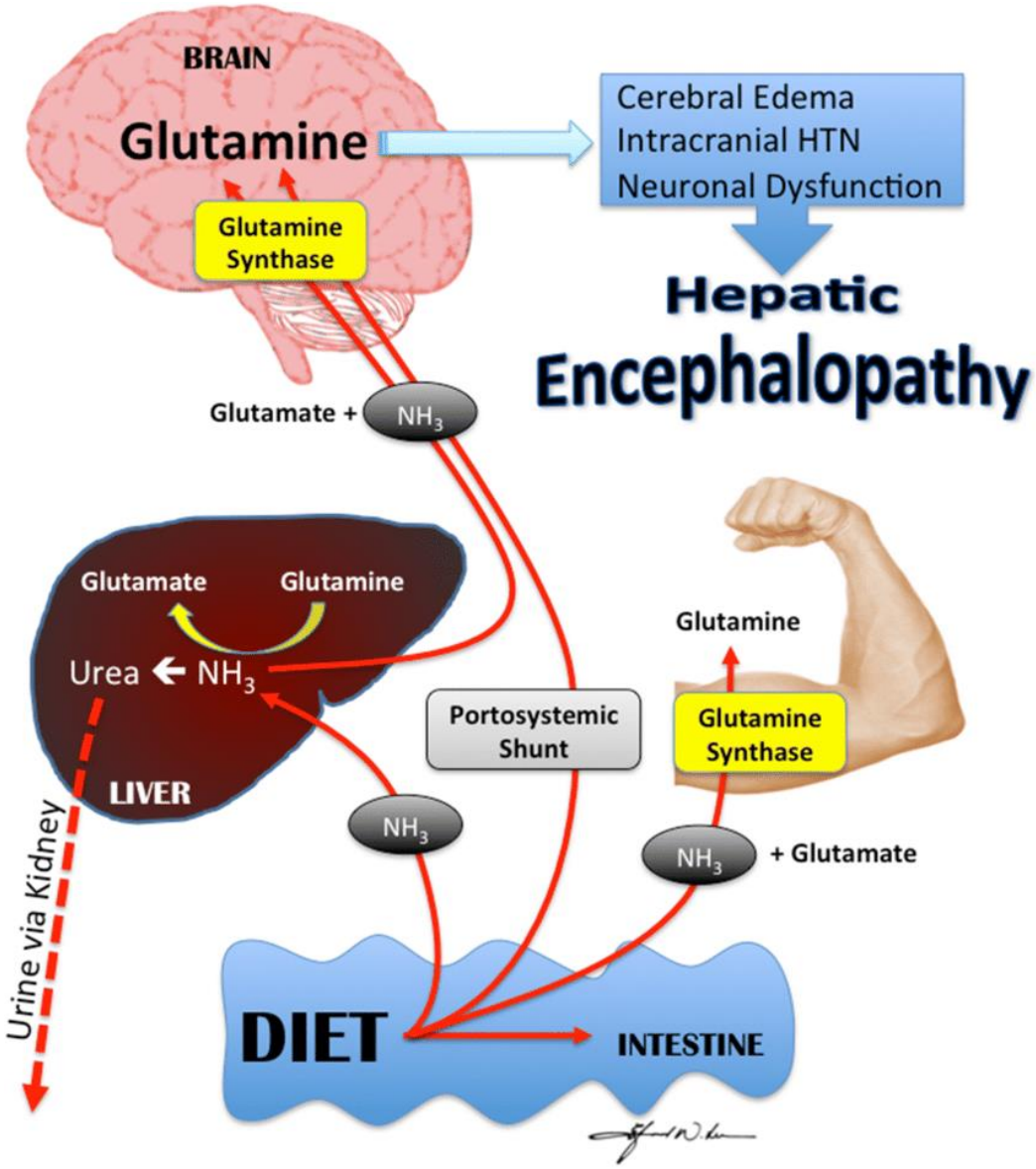

Figure 1: A schematic summary of pathophysiology of hepatic encephalopathy and ammoniogenesis in end-stage liver disease patients. As a result of liver failure and cirrhosis, less ammonia is detoxified in the liver and portosystemic shunting allows a greater amount of ammonia to enter the systemic circulation bypassing the portal system. In cirrhotic patients, ammonia detoxification takes place less in the liver and more in the skeletal muscle and kidney. In liver, ammonia is converted to urea and then excreted through the kidneys and into the colon. In skeletal muscle and kidney, ammonia is converted to glutamine thus enzymatically removing the ammonia. In addition, astrocytes in the brain also play a role in detoxifying ammonia via glutamine synthetase, the increase in ammonia concentrations passing the blood-brain barrier results in an increase in glutamine in the brain and this brings in more water into astrocytes. This swelling of astrocytes leads to cerebral edema and intracranial hypertension, ultimately resulting in neuronal dysfunction
Source: https://doi.org/10.1007/s10620-020-06050-

1.2. ENCEPHALITIS

Is an inflammation that occurs in the brain when a virus in some cases, bacteria attack it directly, and can also be triggered by other factors. It is an inflammatory process of the meninges, the membranes that cover the central nervous system. In some cases, encephalitis can result from an immune system disorder. Mild cases may cause no symptoms or may present with mild flu-like symptoms. Severe cases can be fatal. Immediate medical attention is needed for symptoms such as confusion, hallucinations, seizures, weakness, and loss of sensation (Bale, 2015; Gol *et al.*, 2015; Bohmwald *et al.*, 2021; Greenlee, 2024).

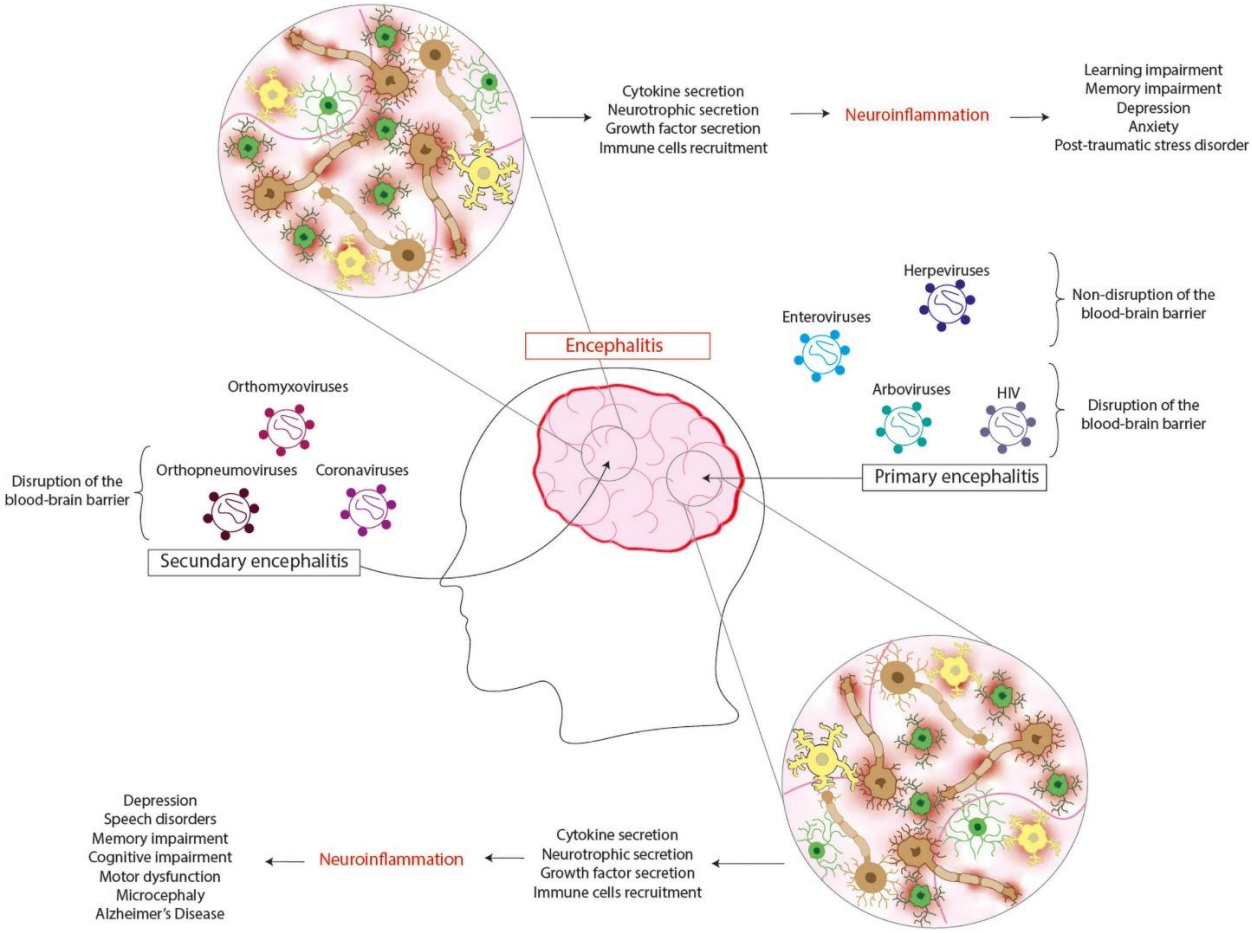

Figure 2: Viral encephalitis leads to several neurological sequelae. Primary encephalitis is caused by viruses that infect the brain as their main target, which can be found in arboviruses, enteroviruses, herpesviruses, and HIV. The infection of cells from the central nervous system induces cytokine, neurotrophic, and growth factor secretion and the recruitment of immune cells. It is thought that this response can contribute to neuroinflammation, leading to neurological sequelae such as depression, speech disorders, memory, and cognitive impairment, motor dysfunction, microcephaly, and even Alzheimer's disease. Secondary encephalitis is caused by viruses that do not infect the brain as their main target, which can be found in orthomyxoviruses, orthopneumoviruses, and coronaviruses. The infection of cells from the central nervous system induces cytokine, neurotrophic, and growth factor secretion and the recruitment of the immune cells. This response contributes to neuroinflammation, leading to neurological sequelae such as learning and memory impairment, depression, anxiety, and post-traumatic stress disorder

Source: https://doi.org/10.3389/fncel.2021.755875

Viruses that cause primary encephalitis invade the brain directly. Arthropods are transmitted to people through the bites of arthropods, mainly mosquitoes, fleas, or ticks. Arboviruses are short for arthropod-borne viruses. Viruses are transmitted by arthropods when they bite infected animals or people. Many species of domestic animals and birds have these viruses. Epidemics occur periodically only in humans when infected mosquitoes or animals increase (Encephalitis Society, 2014; Bale, 2015; Gol *et al.*, 2015; Greenlee, 2024).

Epidemics tend to occur when arthropods bite mosquitoes and ticks, usually during warm weather. The infection spreads from arthropods to people, not from person to person. Viruses that cause primary encephalitis invade the brain directly. These infections may be epidemic due to arboviruses, echoviruses, coxsackieviruses or polioviruses in some developing countries. Sporadic due to cytomegalovirus or herpes simplex virus, varicella-zoster, COVID-19, HIV, lymphocytic choriomeningitis, rabies virus, or mumps virus. Arboviral encephalitis transmitted by mosquitoes infects people during the spring, summer, and early fall when the weather is warm. Some arboviral encephalitis (Figure 3) (Encephalitis Society, 2014; Bale, 2015; Gol *et al.*, 2015; Greenlee, 2024).

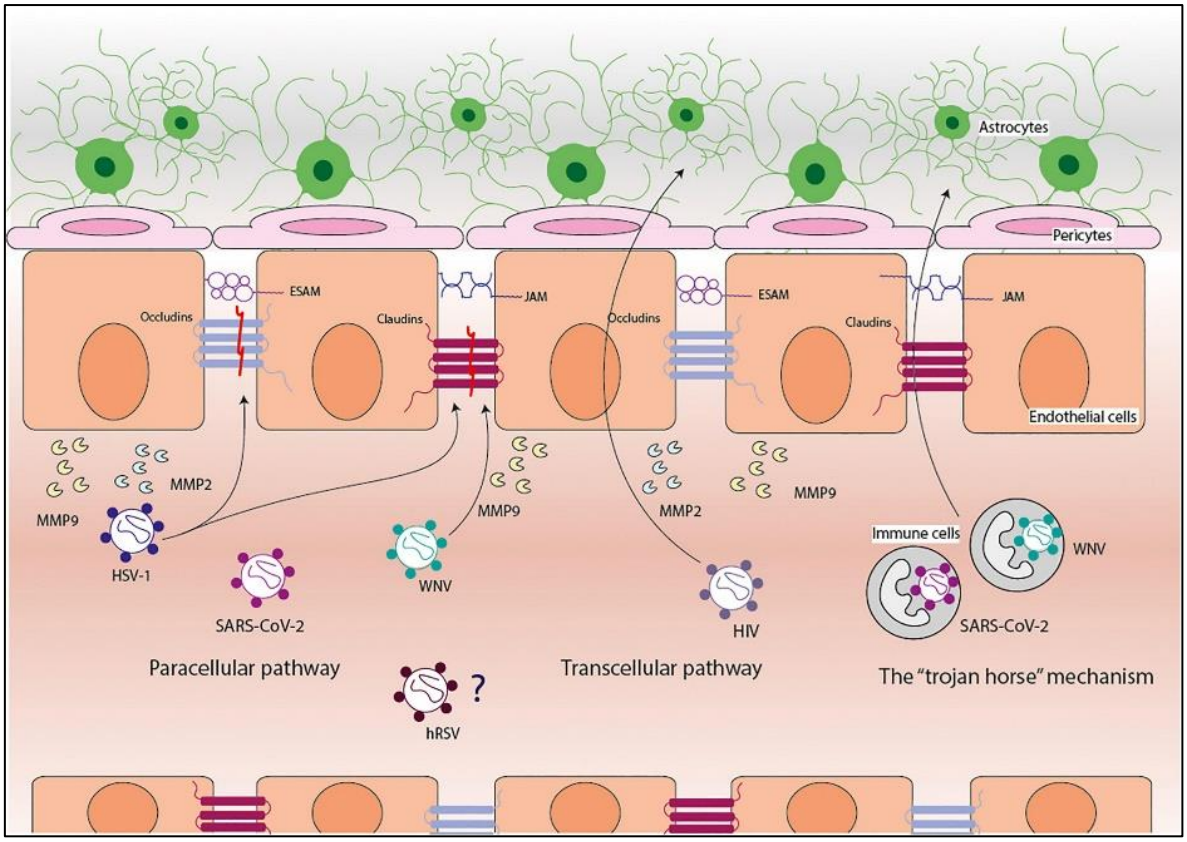

Figure 3: Pathways used by viruses to cross the blood-brain barrier. The blood-brain barrier (BBB) is composed of endothelial cells, pericytes, and astrocytes cells. The viruses use three principal pathways to cross the BBB: paracellular, transcellular, and the "trojan horse" mechanism. West Nile virus (WNV) can reach the central nervous system via the paracellular pathway and the "trojan horse" mechanism, disrupting claudins and promoting the secretion of matrix metalloproteinases (MMPs) 9. Herpes simplex virus (HSV-1) can reach the central nervous system via the paracellular pathway, disrupting claudins and occludins and promoting the secretion of MMP2 and MMP9. Human immunodeficiency virus (HIV) can reach the central nervous system via the paracellular and transcellular pathways and promote the secretion of MMP2 and MMP9. SARS-CoV-2 can reach the central nervous system via the paracellular pathway and the "trojan horse" mechanism; however, it has not been elucidated how and what it promotes. Human respiratory syncytial virus (hRSV) can reach the central nervous system through the disruption of the BBB, but how and what it causes this has not been elucidated yet
Source: https://doi.org/10.3389/fncel.2021.755875

3. OBJECTIVE

This review aims to evaluate the efficiency of neural enolase (NSA) in diagnosing viral encephalitis.

4. METHODS

The methodology used an integrative literature review and a synthesis process to develop the study, expand the understanding of knowledge, and achieve the expected results. The integrative literature review is a method that aims to synthesize results obtained in research on a topic or issue, in a systematic, ordered, and comprehensive way. It is called integrative because it provides broader information on a subject/problem, thus constituting a body of knowledge. To carry out the study, a search for scientific articles was carried out through the Virtual Health Library, in the SCIELO, LILACS, and PUBMED databases, using the terminologies registered in the Health Sciences Descriptors, encephalitis, enolase, virus, and diagnosis.

5. SELECTED STUDIES

Many arboviruses can cause encephalitis. In general, the different types of encephalitis are named according to the location where the virus was discovered or the species of animal that typically transmits it.

5.1. In the United States, mosquitoes spread several types of encephalitis, including:

5.1.1 La Crosse encephalitis is caused by the La Crosse virus (California virus). It is most common in the Midwest but can occur anywhere in the country. This encephalitis accounts for most cases in children. Many are mild and undiagnosed. Less than 1% of people infected with it die (Bale, 2015; Gol *et al.*, 2015; Greenlee, 2024).

5.1.2 Eastern equine encephalitis occurs predominantly in the eastern United States. A few cases have occurred in the Great Lakes region. Eastern equine encephalitis mainly affects young children and people

over the age of in children under one year old, it can cause severe symptoms and permanent damage to the brain and nerves. More than half of those infected die (Bale, 2015; Gol *et al.*, 2015; Greenlee, 2024).

5.1.3 West Nile encephalitis, previously found only in Europe and Africa, first appeared in the New York metropolitan area in 1999. It has spread throughout the United States. Several species of birds can become infected with the virus when they are bitten by an infected mosquito. This encephalitis mainly affects older people. This virus causes a mild infection called West Nile fever, which is much more common. West Nile encephalitis develops in less than 1% of people who develop West Nile fever. About 9% of people with West Nile encephalitis die. However, those who only have West Nile fever usually recover completely (Figure 4) (Bale, 2015; Gol *et al.*, 2015; Koch *et al.*, 2021; Greenlee, 2024).

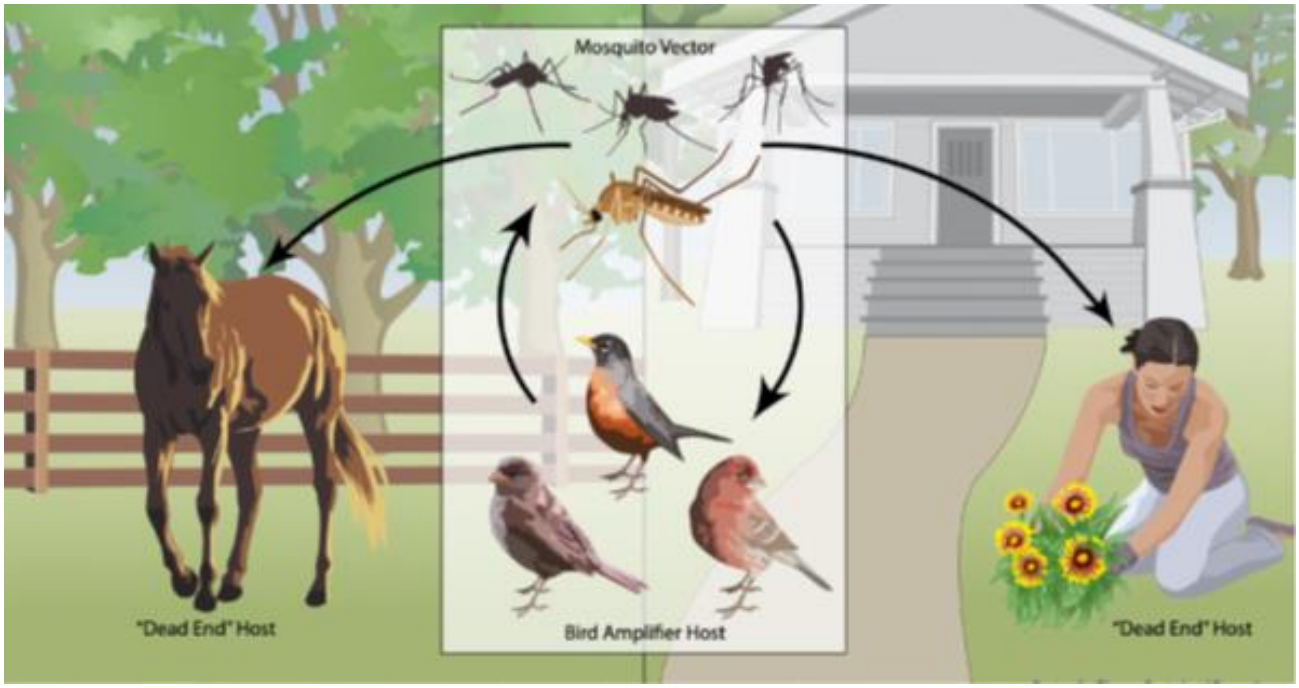

Figure 4: In nature, WNV cycles between mosquitoes and birds. Some bird species develop high levels of the virus in their bloodstream, and mosquitoes can become infected by biting these infected birds, continuing the cycle. Humans are "dead-end" hosts, meaning they don't pass on the virus to other mosquitoes that bite them, because they do not develop high enough levels in the bloodstream
Source: Centers for Disease Control and Prevention - PDF

5.1.4 Saint Louis (Missouri) encephalitis occurs mainly in areas of the central and southeastern United States, but also in western states. The infection is more common in the summer and is more likely to affect the brains of older people. The epidemic has occurred once every 10 years but is now rare (Bale, 2015; Gol *et al.*, 2015; Greenlee, 2024).

5.1.5 Western equine encephalitis can occur in the United States, but for unknown reasons, it has disappeared since 1988. It can affect all age groups but is more severe and is more likely to affect the brains of children under 1 year old (Greenlee, 2024).

5.2. Several types of encephalitis are spread by ticks. These include:

5.2.1 Tick-borne encephalitis occurs in northern Asia, Russia, and Europe. This infection usually causes a mild flu-like illness that clears up within a few days, but some people, usually those 50 years of age or older, develop more severe symptoms. Because many cases occur in Europe and Russia, a vaccine is available there (Greenlee, 2024).

5.2.2. In Lyme disease, the tick must remain attached to the body for 24 to 48 hours to spread the disease. In contrast, Powassan virus infection can be transmitted if an infected tick remains attached to the body for as little as 15 minutes (Figure 5) (Glaser *et al.*, 2006; Wang *et al.*, 2007; Bale, 2015; Greenlee, 2024).

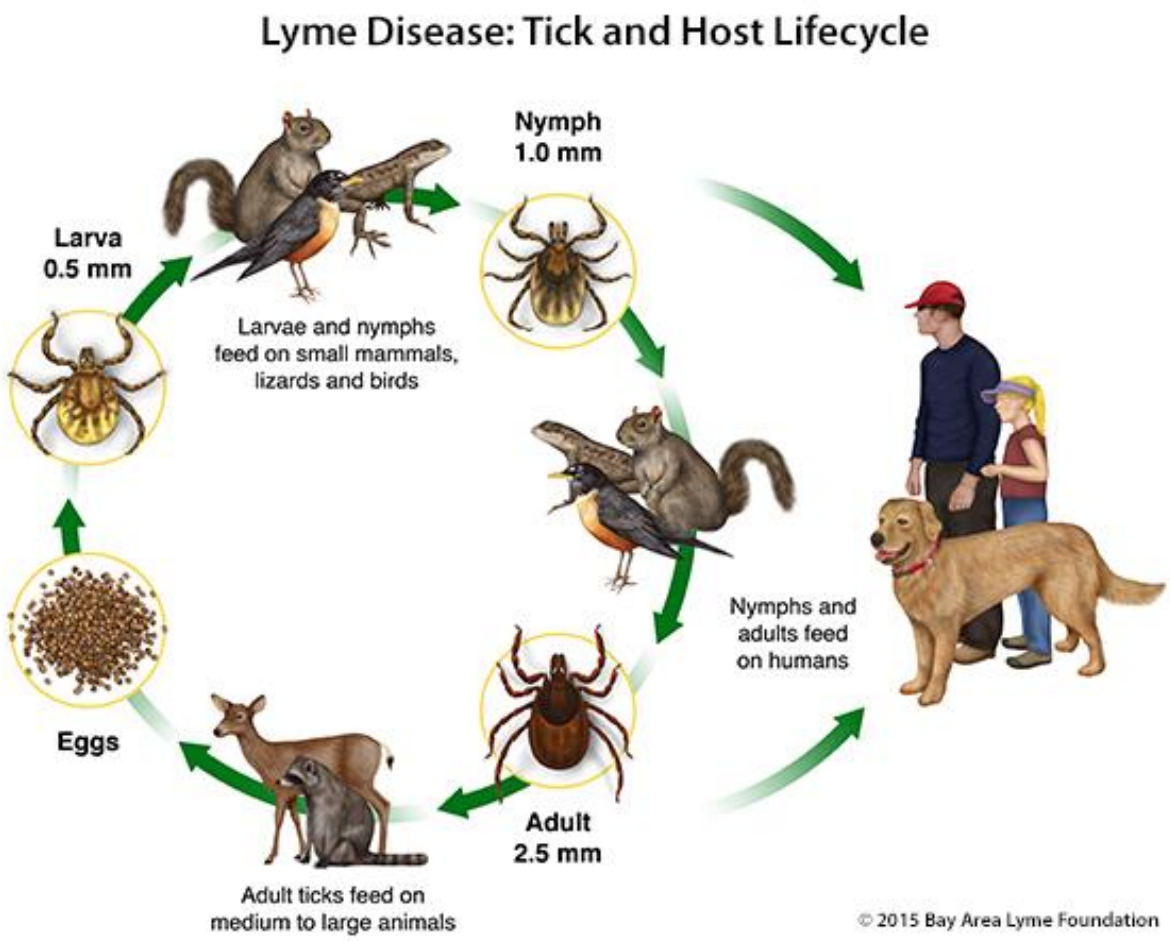

Figure 5: In California, the grey squirrel is the biggest culprit. For example, studies have shown that 86% of tick larvae carrying *Borrelia burgdorferi* (Bb) were infected by the western grey squirre
Source: Hostcycle image courtesy of Emily M. Eng White-footed mouse and Western Fence lizard images courtesy of Anand Varma

5.2.3 Colorado tick fever occurs in areas of the western United States and Canada that are between 4,000 and 10,000 feet above sea level. Colorado tick fever causes a flu-like illness. Occasionally, people with Colorado tick fever develop meningitis or encephalitis. Colorado tick fever rarely causes death. It is rarely transmitted through blood transfusions (Tunkel *et al.*, 2008; Kneen *et al.*, 2012; Greenlee, 2024).

5.3. Mosquito-borne encephalitis

5.3.1 Powassan virus infection occurs mainly in Canada, the Great Lakes region, and the northeastern United States. Powassan virus has also caused cases of encephalitis in Russia. The virus is similar to the one that causes tick-borne encephalitis in Europe. Powassan virus infection usually causes mild or no symptoms. However, the infection can also cause severe encephalitis with headache, vomiting, seizures, loss of coordination, speech problems, or coma. About 10% of people with severe encephalitis die. Powassan virus is spread by deer ticks, which also transmit Lyme disease (Figure 6) (Raval *et al.*, 2012; Gol *et al.*, 2015; Piantadosi *et al.*, 2016; Santos *et al.*, 2016; Zehra and Carpenter, 2017; Greenlee, 2024).

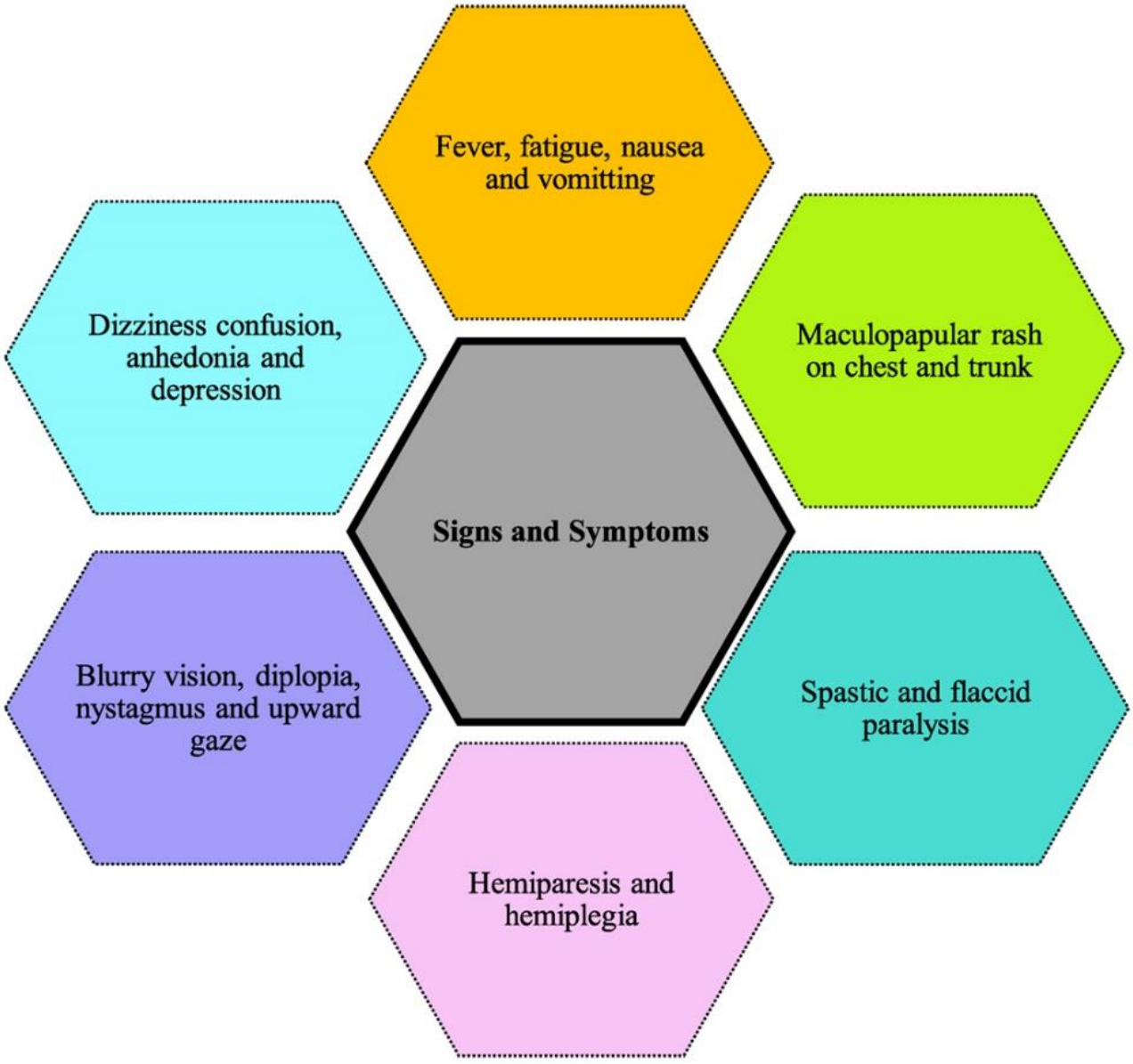

Figure 6: Signs and symptoms of Powassan virus

Sources: DOI and References: doi: 10.3390/v8080220 (32), doi:10.1093/cid/civ1005 (34) doi: 10.1186/1756-0500-5-594 (35) and https://doi.org/10.3389/fpubh.2017.00342

5.3.2 Chikungunya virus

Chikungunya virus was first identified in Africa but has spread to several countries. Most people with Chikungunya disease feel better within a week. However, chikungunya disease can result in severe encephalitis and even death, especially in infants and people over 65 years of age (Costa and Sato, 2020; Greenlee, 2024).

5.3.3 Japanese encephalitis virus

Japanese encephalitis virus is a common cause of encephalitis in Asia and the western Pacific. In the United States, Japanese encephalitis occurs only in travelers (Costa and Sato, 2020; Greenlee, 2024).

5.3.4 Venezuelan equine encephalitis

Venezuelan equine encephalitis occurs mainly in South and Central America. Venezuelan equine encephalitis virus caused an encephalitis epidemic in Texas in 1971, but it rarely causes encephalitis in the United States today. It occurs mainly in travelers returning from areas where the virus is common (Figure 7) (Costa and Sato, 2020; Greenlee, 2024).

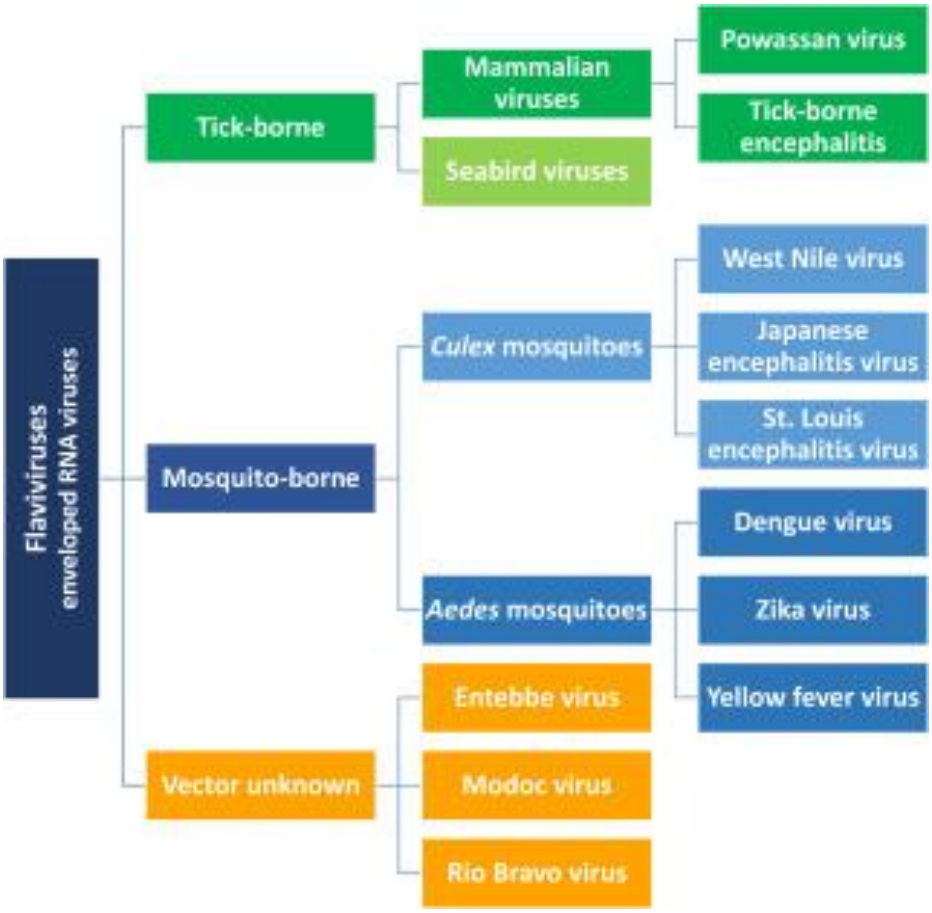

Figure 7: Classification of selected flavivirus. Flaviviruses are enveloped RNA viruses transmitted by arthropods that can be classified by the vector of transmission (i.e. mosquito, tick, and unknown) and by whether they infect mammals or other animals

Source: DOI: https://doi.org/10.1016/j.modpat.2023.100188

5.3.5 Zika virus

Zika virus was first identified in the Zika forest in Uganda and has since spread to other countries. Zika infection can cause fever, joint and muscle pain, headaches, and a red, raised rash. Getting Zika virus infection during pregnancy can cause microcephaly and severe brain damage in the baby (Costa and Sato, 2020; Hale, 2023; Greenlee, 2024).

5.4. Definition of encephalitis for other authors:

In acute encephalitis, inflammation, and edema occur in infected areas throughout the cerebral hemispheres, brain stem, cerebellum, and occasionally the medulla. Petechial hemorrhages may be present in severe infections. Direct viral invasion of the brain often damages neurons, sometimes producing microscopically visible inclusion bodies. Severe infection, particularly untreated herpes simplex virus (HSV) encephalitis, can cause hemorrhagic necrosis of the brain (Kennedy, 2004; Costa and Sato, 2020). Others virus:

5.4.1 Varicella zoster virus (VZV) encephalitis

In children, VZV encephalitis usually occurs concomitantly with chickenpox. However, it may occur as a reactivation of a previous infection without skin lesions. Lesions may be present in the gray matter, white matter, and their transition. Most lesions are ischemic, but hemorrhagic lesions may also occur along with areas of stenosis in small and large vessels (De Broucker *et al.*, 2012; Costa and Sato, 2020).

5.4.2 Enterovirus encephalitis

The second most common cause of viral encephalitis after the Herpesviridae family. There have been several reports of outbreaks of encephalitis caused by enteroviruses in the summer. Patients usually present with diarrhea and vomiting, and, depending on the serotype of the virus, may present with hand-foot-and-mouth disease, herpangina, or other types of rashes (Perez-Velez *et al*., 2007; Casas-Alba *et al*., 2017; Costa and Sato, 2020).

5.4.3 O herpes-vírus simples (herpes-vírus humanos tipos 1 e 2)

According to data released by the World Health Organization (WHO), together with the Brazilian Society of Dermatology, more than 90% of the adult Brazilian population already has the herpes virus in their bodies. However, only 10 to 15% show symptoms. Despite the same name, herpes (Herpes Simplex Virus,

HSV) has two types of viruses that spread differently. Herpes simplex is the most common viral disease in modern humans, excluding respiratory infections. In immunocompromised patients, herpes infections can cause several complications. Herpes simplex is also classified as a sexually transmitted disease, affecting only men and without seasonal variation (Silverman *et al.,* 2002; Trindade *et al.,* 2007; Santos *et al.,* 2012)

5.4.4 Human herpesvirus 6 (HHV-6)

The common collective name for Human beta herpes virus 6A (HHV-6A) and Human beta herpes virus 6B (HHV-6B). These closely related viruses are two of the new herpesviruses known to have humans as their primary host. Three stages can be recognized in the natural history of HHV-6 infection. The first is represented by acute primary infection in infants. The second stage occurs in healthy children and adults; the virus replicates in the salivary glands and is secreted into saliva as HHV-6B without inducing any obvious pathology, remains latent in at least lymphocytes and monocytes, and persists in various tissues, possibly with low-level replication. The third stage occurs infrequently, usually in immunocompromised individuals, and is linked to the reactivation of the virus by latency or reinfection. Other pathological conditions, notably multiple sclerosis, tumors, and CFS, have been associated with HHV-6 (Caserta *et al.,* 2001; Despensa and Medveczky, 2017; Eliassen *et al.,* 2018).

It usually causes recurrent infections affecting the skin, oral cavity, lips, eyes, and genitals. Serious infections commonly include encephalitis, meningitis, neonatal herpes, and, in patients who are immunocompromised, disseminated infection. Mucocutaneous infections produce clusters of small, painful vesicles on an erythematous base (Silverman *et al.,* 2002; Trindade *et al.,* 2007; Santos *et al.,* 2012).

5.4.5. Influenza

Influenza encephalitis has phenotypes of variable severity. It can present as mild encephalopathy, malignant cerebral edema, and acute necrotizing encephalopathy. Neurologic symptoms seizure, altered or loss of consciousness, decreased cognitive processing speed, motor paralysis or sensory loss, and abnormal behavior develop approximately two days after systemic symptoms fever, myalgia, and respiratory symptoms). There is evidence that the influenza A (H1N1) strain may cause more neurologic manifestations than seasonal influenza (flu) (Wang *et al.,* 2010; Kneenet *al.,* 2012; Costa and Sato, 2020).

5.4.6. Measles encephalitis

Measles encephalitis may be characterized by mild symptoms with brain MRI showing reversible lesions in the splenium of the corpus callosum. These may be seen in influenza encephalitis, as mentioned above. It usually occurs in immunocompetent individuals who acquired the infection before vaccination, causing widespread demyelination of the CNS and neuronal loss. Neurological symptoms include intellectual deterioration, personality changes and behavioral abnormalities, weakness, rigidity, myoclonus, and autonomic failure (Gutierrez *et al.,* 2010; Holtet *et al.,* 2016; Costa and Santo, 2024).

5.4.7. Epstein-Barr Virus (EBV)

It is a human herpesvirus that participates in the etiology of many autoimmune diseases and cancers. The presentation of infection in the central nervous system can vary from asymptomatic to fatal. Viral encephalitis is a challenge in medical practice and is often underdiagnosed. EBV is rarely seen causing this type of disease in adults with HIV (Landim Filho *et al.,* 2023).

5.5. Autoimmune encephalitis

The most common viruses involved include enteroviruses, Epstein-Barr virus, hepatitis A or hepatitis B virus, human immunodeficiency virus (HIV), and influenza viruses. Before childhood immunization became widespread, the viruses that cause measles, rubella, chickenpox, and mumps were common causes of acute disseminated encephalomyelitis. This type of encephalitis can also occur in people with cancer or other (Costa and Sato, 2020; Greenlee, 2024).

5.6. Autoimmune disorders

Autoimmune encephalitis can also develop if the immune system produces antibodies that attack proteins on the surface of nerve cells called N-methyl-d-aspartate (NMDA) receptors. The resulting encephalitis is called anti-NMDA receptor encephalitis. Some evidence suggests that anti-NMDA receptor encephalitis is a more common type of encephalitis than previously thought. It occasionally develops after encephalitis due to the herpes simplex virus, even after that encephalitis has been successfully treated (Greenlee, 2024).

5.7. Diagnosis of encephalitis

The diagnosis of encephalitis is based on anamnesis and physical examination, which can be complemented with neuroimaging and cerebrospinal fluid analysis. In addition, other tests that can be used to aid diagnosis are Electroencephalograms and laboratory tests (especially serology) (Costa and Sato, 2020).

5.8. Encephalitis treatment

5.8.1. Antibiotics for encephalitis caused by bacteria.
5.8.2. Antivirals for encephalitis caused by viruses.
5.8.3. Steroids to reduce swelling in the brain.
5.8.4. Anticonvulsants to prevent seizures.
5.8.5. Painkillers to relieve headache and fever.

Treatment aims to combat the infection and includes rest, fluid intake, use of corticosteroids, anticonvulsants, and adequate nutrition (Costa and Sato, 2020).

7. Enolase (phosphorylate hydratase, NSE, neuron-specific enolase)

Enolase is an enzyme found in central and peripheral neurons, fetal lung tissue, and adult neuroendocrine structures, and its function is to catalyze the transformation of 2-phosphoglycerate into phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer isomers (alpha, beta, and gamma). Neuron-specific enolase (NSE) is a gamma homodimer of 78 kD and represents the dominant enolase isoenzyme found in neuronal and neuroendocrine tissues. Its levels in tissues other than erythrocytes are negligible. The biological half-life of NSE in body fluids is approximately 24 hours (Figure 8-10) (Haque *et al.*, 2016; Stancioiu *et al.*, 2023; Fleury S.A., 2024).

Its measurement is useful for monitoring tumors of neuroendocrine origin, such as neuroblastoma, pheochromocytoma, medullary thyroid carcinoma, small cell lung carcinoma, melanoma, and some pancreatic tumors. NSE concentrations in cerebrospinal fluid (CSF) are often elevated in diseases that result in relatively rapid neuronal destruction (Hajduková *et al.*, 2015; Gushue *et al.*, 2018; Zamproni *et al.*, 2019).

NSE is used in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias such as Creutzfeldt-Jakob disease (CJD). NSE may also be useful as a prognostic marker in neuronal injury. For example, there is increasing evidence that elevated serum NSE levels correlate with poor outcomes in coma, particularly when caused by hypoxic insult. Central nervous system metastases from small-cell lung carcinoma, particularly if they involve the leptomeninges, also cause elevations in CSF NSE concentrations (Figure 11) (Fujii *et al.*, 2005; Raghunathan *et al.*, 2014).

In addition to being produced by astrocytes, melanocytes, and adipose cells, NSE is increased and is associated with damage to the blood-brain barrier found in SAE. In addition, increased serum levels of NSE occur in situations of rapid and acute neuronal destruction, such as acute post-traumatic brain injury, post-cardiac arrest, perinatal asphyxia, intracerebral hemorrhage, septic shock, infections, cardiopulmonary resuscitation, autoimmune disorders, and neuroblastomas, with possible neuronal alterations and death (Figure 12) (Fujii *et al.*, 2005; Jung *et al.*, 2013; Sawada *et al.*, 2016; Fleury S.A., 2024).

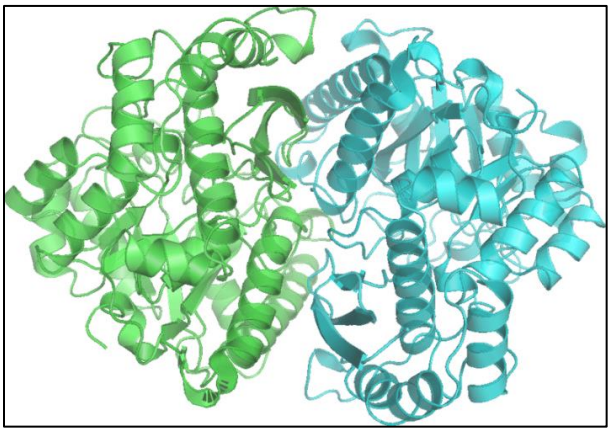

Figure 8: Yeast enolase dimer
Source: https://en.wikipedia.org/wiki/Enolase

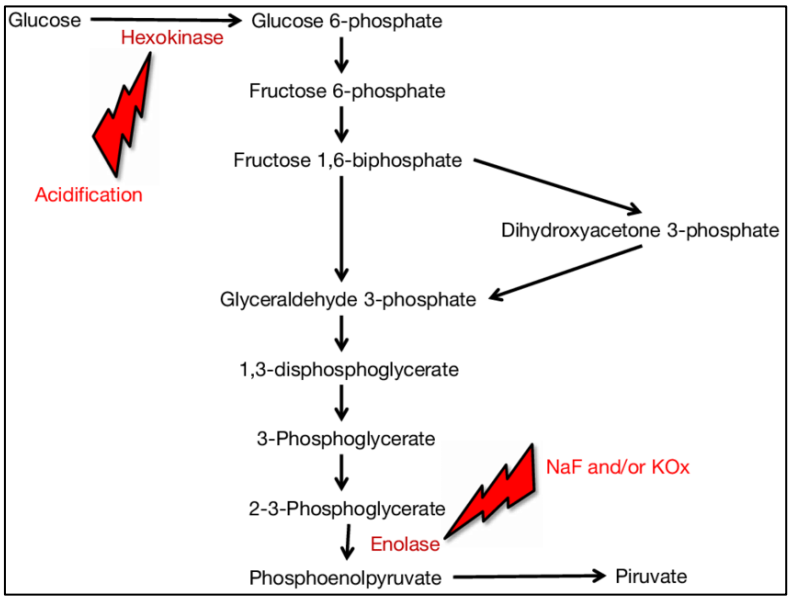

Figure 9: Effect of hexokinase and enolase inhibition in the glycolytic pathway. NaF, sodium fluoride; Kox and potassium oxalate
Source: https://www.researchgate.net/figure/Effect-of-hexokinase-and-enolase-inhibition-in-the-glycolytic-pathway-NaF-sodium_fig2_317165805

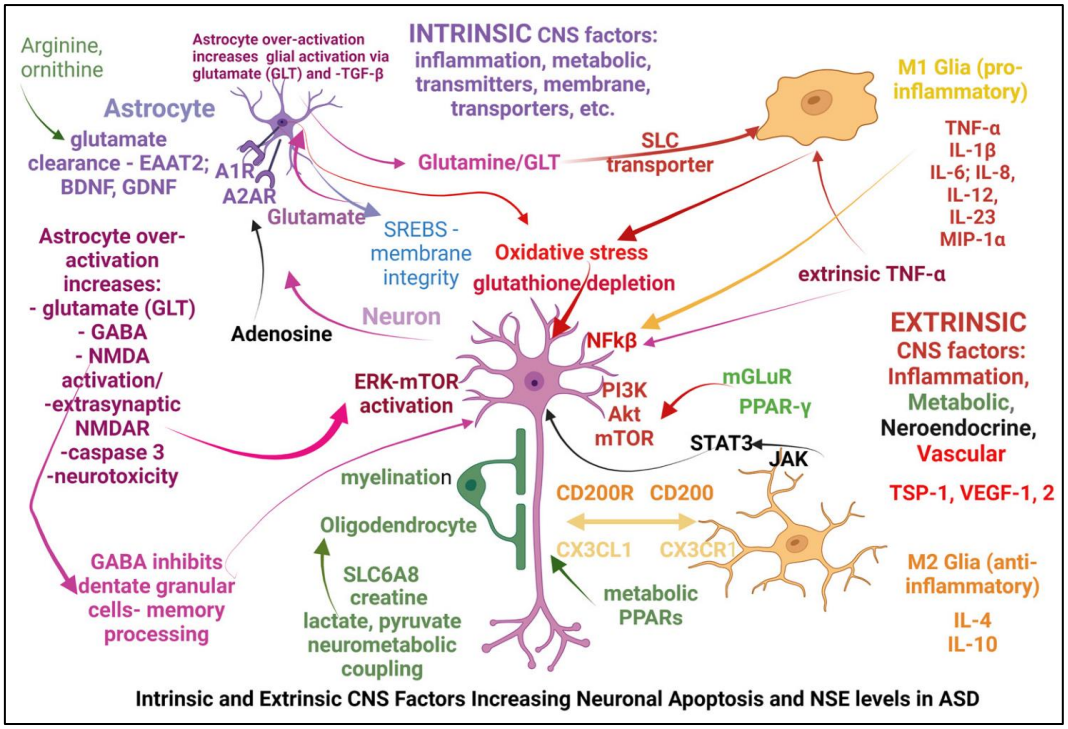

Figure 10: Elevated NSE levels resulting from neuronal apoptosis induced by intrinsic and extrinsic CNS factors
Source: https://doi.org/10.3390/life13081736

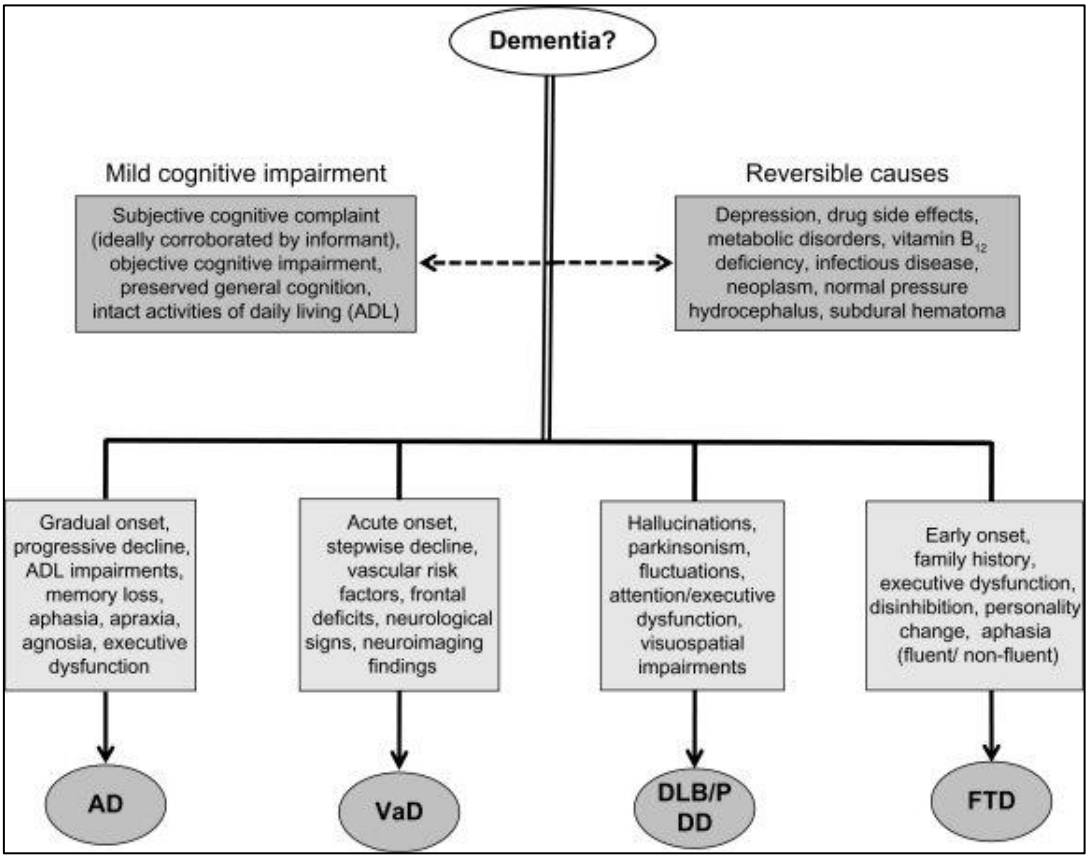

Figure 11: Enolsae: Differential diagnostic considerations for dementia. Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia; VaD, vascular dementia
Source: https://www.researchgate.net/figure/Differential-diagnostic-considerations-for-dementia-Abbreviations-AD-Alzheimers_fig3_51203401

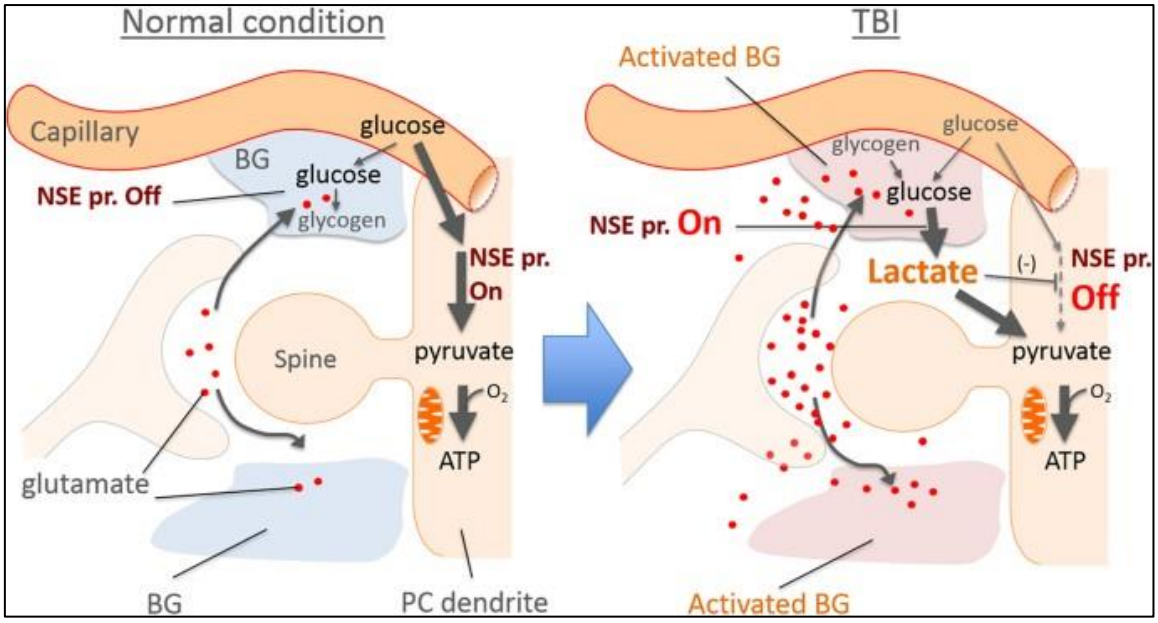

Figure 12: Schematic depicting a possible mechanism regulating the epigenetic switch of the NSE promoter in BG and PCs. In normal conditions, PCs use glucose as a primary energy resource, which is metabolized to pyruvate via the glycolysis pathway, which involves the glycolytic enzyme NSE (NSE promoter is ON). The pyruvate is oxidized and enters the tricarboxylic (TCA) cycle in the mitochondria to generate ATP. In traumatic brain injury, high amounts of glutamate are released from injured cells, which in turn excites neurons to further release the glutamate. The excess amount of extracellular glutamate is taken up by BG that was activated by cytokines released from activated microglia. In the activated BG, the NSE promoter is activated to produce the NSE, which converts glucose into lactate, with the subsequent transfer of lactate to neurons (astrocyte-neuron lactate shuttle). The lactate inhibits glycolysis in the PCs through hydroxycarboxylic acid receptor 1 (HCA1), leading to suppression of the NSE promoter activity in PCs and facilitating lactate metabolization into pyruvate
Source: https://doi.org/10.1038/srep27758

8. CONCLUSION

Encephalitis can be triggered by several types of etiologies, making the epidemiology of the disease dependent on the etiological type. Thus, the following etiologies are possible: infectious, post-infectious, autoimmune, and paraneoplastic. NSE is used in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias. NSE may also be useful as a prognostic marker in neuronal injury. For example, there is increasing evidence that elevated serum NSE levels correlate with poor outcomes in coma, particularly when caused by hypoxic insult.

REFERENCES

- ABCMED. (2017). Encephalopathy - what are the symptoms? What should we know? Retrieved July, 27, 2024 from https://www.abc.med.br/p/sinais.-sintomas-e-doencas/1303718/encephalopathy-quais-os-sintomas-o-que-devemos-saber.htm>
- Bale, Jr. J. F. (2015). Virus and immune-mediated encephalitides: epidemiology, diagnosis, treatment, and prevention. *Pediatric Neurology*, *53*(1), 3-12.
- Bohmwald, K., Andrade, C. A., Gálvez, N. M., Mora, V. P., Muñoz, J. T., & Kalergis, A. M. (2021). The causes and long-term consequences of viral encephalitis. *Frontiers in Cellular Neuroscience*, *15*, 755875.
- Casas-Alba, D., De Sevilla, M. F., Valero-Rello, A., Fortuny, C., García-García, J. J., Ortez, C., ... & Launes, C. (2017). Outbreak of brainstem encephalitis associated with enterovirus-A71 in Catalonia, Spain (2016): a clinical observational study in a children's reference centre in Catalonia. *Clinical Microbiology and Infection*, *23*(11), 874-881.
- Caserta, M. T. D. J., Simulado, Y., & Dewhurst, S. (2001). Human herpesvirus 6. *Clinical Infectious Diseases*, *33*(6), 829-833.
- Costa, B. K., & Sato, D. K. (2020). Viral encephalitis: a practical review on diagnostic approach and treatment. *Journal of Pediatrics*, *96*(S1), 12-19.
- De Broucker, T., Mailles, A., Chabrier, S., Morand, P., & Stahl, J. P. (2012). Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case series of 20 patients. *Clinical Microbiology and Infection*, *18*, 808-819.
- Despensa, S. N., & Medveczky, P. G. (2017). Latency, integration, and reactivation of human herpesvirus-6. *Virus*, *9*, 7.
- Eliassen, E., Lum, E., Pritchett, J., Ongradi, J., Krueger, G., Crawford, J. R., ... & Hudnall, S. D.

(2018). Human herpesvirus 6 and malignancy: a review. *Frontiers in Oncology*, *8*, 512.

- Encephalitis Society. (2014). World Encephalitis Day. Retrieved July, 27, 2024 from https://bvsms.saude.gov.br/22-02-dia-mundial-da-encefalite/
- Fleury, S. A. (2024). Neuronal-specific enolase, NSE. Retrieved July 17, 2024 from https://www.fleury.com.br/medico/exames/herpes-simplex-i/ii-anticorpos-igg-e-igm-soro.
- Fujii, A., Yoneda, M., Ito, T., Yamamura, O., Satomi, S., Higa, H., ... & Kuriyama, M. (2005). Autoantibodies against the amino terminal of α-enolase are a useful diagnostic marker of Hashimoto's encephalopathy. *Journal of Neuroimmunology*, *162*(1-2), 130-136.
- Gold, J. J., Crawford, J. R., Glaser, C., Sheriff, H., Wang, S., & Nespeca, M. (2014). The role of continuous electroencephalography in childhood encephalitis. *Seminars in Pediatric Infectious Diseases*, *50*, 318-23.
- Greenlee, J. E. (2024). Encephalitis. MSD Manual. Retrieved July 20, 2024 from https://www.msdmanuals.com/pt-br/profissional/dist%C3%BArbios-neurol%C3%B3gicos/infec%C3%A7%C3%B5es-encef%C3%A1licas /encefalite
- Gross, J. S. (2024). Encephalopathies: types and treatments. Retrieved July, 28, 2024 from https://blog.medcel.com.br/post/encefalopatias-tipos-e-tratamentos
- Gushue, D., Herbst, A., Sim, V., McKenzie, D., & Aiken, J. M. (2018). 14-3-3 and enolase abundances in the CSF of Prion diseased rats. *Prion*, *12*(3-4), 253–260.
- Gutierrez, J., Issacson, R. S., & Koppel, B. S. (2010). Subacute sclerosing panencephalitis: an update. *Developmental Medicine & Child Neurology*, *52*, 901-907.
- Hajduková, L., Sobek, O., Prchalová, D., Bílková, Z., Koudelková, M., Lukášková, J., & Matuchová, I. (2015). Biomarkers of brain damage: S100B and NSE concentrations in cerebrospinal fluid—a normative study. *BioMed Research International*, *2015*(1), 379071.
- Hale, G. L. (2023). Flaviviruses and the traveler: Around the world and to your stage. A review of West Nile, yellow fever, dengue, and zika viruses for the practice. *Pathologist*, *36*(6), 100188.
- Haque, A., Ray, S. K., Cox, A., & Banik, N. L. (2016). Neuron-specific enolase: a promising therapeutic target in acute spinal cord injury. *Metabolic Brain Disease*, *31*(3), 487-495.
- Holt, R. L., Kann, D., Rassbach, C. E., Schwenk, H. T., Ritter, J. M., Rota, P. A., & Elbers, J. (2016). Subacute sclerosing panencephalitis: the foothold in undervaccination. *The Journal of Pediatrics*, *179*, 259-262.
- Jung, D. W., Kim, W. H., Park, S. H., Lee, J., Kim, J., Su, D., ... & Williams, D. R. (2013). A unique small molecule inhibitor of enolase clarifies its role in fundamental biological processes. *ACS Chemical Biology*, *8*(6), 1271-1282.
- Kneen, R., Michael, B. D., Menson, E., Mehta, B., Easton, A., Hemingway, C., ... & Solomon, T. (2012). Management of suspected viral encephalitis in children–Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. *Journal of Infection*, *64*(5), 449-477.
- Kennedy, P. G. (2004). Viral encephalitis: causes, differential diagnosis, and management. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*, 110-115.
- Koch, M., Pozsgai, É., Soós, V., Nagy, A., Girán, J., Nyisztor, N., ... & Varga, C. (2021). Identifying risks for severity of neurological symptoms in Hungarian West Nile virus patients. *BMC Infectious Diseases*, *21*, 1-13.
- Landim Filho, P. C. (2023). Epstein-Barr virus encephalitis in an adult patient living with HIV. *Brazilian Journal of Infectious Diseases*, *27*(S1), 103002.
- Lee, E. W., Lee, A. E., Saab, S., & Kee, S. T. (2020). Retrograde transvenous obliteration (RTO): a new treatment option for hepatic encephalopathy. *Digestive Diseases and Sciences*, *65*, 2483-2491.
- Licor Senne. (2024). Neuronal specific enolase, NSE. Retrieved July, 18, 2024 from https://senneliquor.com.br/exame/enolase-especifica-neuronal-nse/#:~:text=A%20enolase%20%C3%A9%20uma%20enzima,alfa%2C %20beta%20e%20gama).
- Lucas, S. M., Rothwell, N., & Gibson, R. (2006). The role of inflammation in CNS injury and disease. *British Journal of Pharmacology*, *147*, S232-S240.
- Pacheco, L. R., Tavares, H. M., Moysés Neto, M., Dantas, M., Rocha, L. S. D. O., Ribeiro, K. M., & Figueiredo, J. F. D. C. (2005). Acute renal failure related to intravenous acyclovir. *Revista da Associação Médica Brasileira*, *51*, 275-278.
- Pancholi, V. (2001). Multifunctional alpha-enolase: its role in diseases. *Cellular and Molecular Life Sciences*, *58*(7), 902–920.
- Pérez-Vélez, C. M., Anderson, M. S., Robinson, C. C., McFarland, E. J., Nix, W. A., Pallansch, M. A., ... & Glodé, M. P. (2007). Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. *Clinical Infectious Diseases*, *45*(8), 950-957.
- Piantadosi, A., Rubin, D. B., McQuillen, D. P., Hsu, L., Lederer, P. A., Ashbaugh, C. D., ... & Lyons, J. L. (2016). Emerging cases of Powassan virus encephalitis in New England: clinical presentation, imaging, and review of the literature. *Clinical Infectious Diseases*, *62*(6), 707-713.

- Raval, M., Singhal, M., Guerrero, D., & Alonto, A. (2012). Powassan virus infection: case series and literature review from a single institution. *BMC Research*, *5*, 594.
- Rech, T. H., Vieira, S. R. R., & Brauner, J. S. (2006). Serum Neuron-Specific Enolase as a prognostic marker after a cardiac arrest. *Brazilian Journal of Intensive Care*, *18*(4), 396-401.
- Santos, M. P. D. M., Morais, M. P. L. D. A., Fonseca, D. D. D., Faria, A. B. S. D., Silva, I. H. M., Carvalho, A. A., & Leão, J. C. (2012). Human herpes virus: types, oral manifestations and treatment. *Odontologia Clínico-Científica (Online)*, *11*(3), 191-196.
- Santos, R. I., Hermance, M. E., Gelman, B. B., & Thangamani, S. (2016) Spinal cord ventral horns and lymphoid organ involvement in Powassan virus infection in a mouse model. *Viruses*, *8*(8), 220.
- Sawada, Y., Konno, A., Nagaoka, J., & Hirai, H. (2016). Inflammation-induced reversible switch of the neuron-specific enolase promoter from Purkinje neurons to Bergmann glia. *Scientific Reports*, *6*(1), 27758.
- Silverman, S. Jr., Eversole, L. R., & Truelove, E. L. (2002). Fundamentals of oral medicine. Rio de Janeiro: Guanabara Koogan.
- Shutterstock. (2024). Peterschreiber.media. Retrieved July, 28, 2024 from https://www.shutterstock.com/pt/image-illustration/man-headache-stroke-3d-illustration-1423084877
- Stancioiu, F., Bogdan, R., & Dumitrescu, R. (2023). Neuron-specific enolase (NSE) as a biomarker for autistic spectrum disease (ASD). *Life*, *13*(8), 1736.
- Tholey, D. (2023). Hepatic encephalopathy. Retrieved July, 28, 2024 from https://www.msdmanuals.com/pt-br/casa/doen%C3%A7as-hep%C3%A1ticas-e-da-ves%C3%ADcula-biliar/manifesta%C3%A7%C3%B5es-da-doen%C3%A7a-hep%C3%A1tica/encefalpatia-hep%C3%A 1tica
- Trindade, A. K, F., Queiroga, A. S., Silva, D. S. C., Campos, S. E. M., Lucena, L. B. S., & Sousa, E. M. D. (2007). Herpes simplex labialis - a therapeutic challenge. *Health Sciences Communication*, *18*(4), 307-314.
- Tunkel, A. R., Glaser, C. A., Bloch, K. C., Sejvar, J. J., Marra, C. M., Roos, K. L., ... & Whitley, R. J. (2008). The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *47*, 303-327.
- Wang, I. J., Lee, P. I., Huang, L. M., Chen, C. J., Chen, C. L., & Lee, W. T. (2007). The correlation between neurological evaluations and neurological outcome in acute encephalitis: a hospital-based study. *European Journal of Pediatric Neurology*, *11*, 63-69.
- Wang, G. F., Li, W., & Li, K. (2010). Acute encephalopathy and encephalitis are caused by influenza virus infection. *Current Opinion in Neurology*, *23*, 305-311.
- Venkatesan, A., Tunkel, A. R., Bloch, K. C., Lauring, A. S., Sejvar, J., Bitnun, A., ... & Cherry, J. (2013). Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clinical Infectious Diseases*, *57*(8), 1114-1128.
- Whitley, R. J., & Kimberlin, D. W. (2005). Herpes simplex encephalitis: children and adolescents. *Seminars in Pediatric Infectious Diseases*, *16*, 17-23.
- Zamproni, L. N., Grinet, M. A., Mundim, M. T., Reis, M. B., Galindo, L. T., Marciano, F. R., ... & Porcionatto, M. (2019). Rotary jet-spun porous microfibers as scaffolds for stem cells delivery to central nervous system injury. *Nanomedicine: Nanotechnology, Biology and Medicine*, *15*(1), 98-107.
- Zehra, F. Z., & Carpenter, D. O. (2017). Powassan Virus—A new reemerging tick-borne disease. *Frontiers in Public Health*, *5*, 342.