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ABSTRACT
Viral encephalitis represents a medical emergency that requires prompt diagnosis and proper management. Patient presentation includes fever, headache, mental status changes, and seizures in different combinations. While herpes simplex virus is the most common cause of sporadic encephalitis worldwide, certain arboviral (arthropod borne) infections remain a health challenge in certain parts of the globe. Zika virus has been recently added to the list of potential offenders. Despite important advances in technology, a substantial percentage of encephalitis cases still remain without a specific diagnosis. Cerebrospinal fluid analysis with viral nucleic acid detection by PCR and neuroimaging are paramount in diagnosing encephalitis and establishing a specific viral etiology. Empiric therapy with acyclovir is required in suspected cases of encephalitis, and maintained for 3 weeks upon confirmation of herpetic etiology. Without specific therapy, herpes encephalitis conveys high mortality and morbidity rates. General support measures are also critical and have been defined in pertinent guidelines. The present review addresses the most common encephalitis in adults and their diagnostic and therapeutic modalities.

1.INTRODUCTION

Acute encephalitis is a medical emergency syndrome of diverse etiologies, mostly viral, that vary depending on location and seasonality (TABLE 1). Despite considerable progress in the diagnostic techniques, a substantial number of cases defy all attempts at identifying a specific cause (Schmidt, Buhler et al. 2011).
Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are identified as the leading cause of encephalitis in Europe and North America (Kennedy 2005, Ambrose, Granerod et al. 2011, Booss and Tselis 2014). Immigration and international travel have led us to face infections that were previously only common in particular geographic regions. That was the case of West Nile encephalitis, an arbo virus confined to a few areas in Africa for years that made its expansion and westward spread in the 90's, reaching the western hemisphere for the first time in 1999. A similar scenario is currently being offered by Zika virus with its recent outbreak in Brazil and its broad afterwards extension.
Although the basic clinical features of most types of viral encephalitis are generally similar, specific findings on examination may help narrow the possible etiologies (TABLE 2).
The most important features in the management of patients with acute viral encephalitis, as well as the key characteristics of the most common infections are reviewed in this manuscript. Despite the absence of specific antiviral therapies in many cases of viral encephalitis, it is essential to provide supportive therapy in all cases. Current guidelines on the management of patients with viral encephalitis are also detailed at the end of this manuscript.

2.HERPES SIMPLEX VIRUS

Herpes simplex virus type 1 (HSV-1) is the single most frequent cause of sporadic encephalitis around the world, although in certain locations local agents should be considered such as West Nile virus or tick-borne encephalitis among others.

Correct and early diagnosis and treatment has a dramatic effect upon survival and reduces the risk of permanent brain injury (Hjalmarsson, Blomqvist et al. 2007). Patients require intense care measures with special emphasis on respiratory problems secondary to a depressed level of consciousness, seizures and intracranial hypertension due to cerebral edema.

2.1. **Epidemiology**

Viral encephalitis is relatively uncommon, with a reported incidenceof 1.5 cases/ 100,000 in England (Granerod, Cunningham et al. 2010). HSV accounts for approximately 10 to 20 percent of the 20 000 annual viral encephalitis in the United States. HSV-1 and HSV-2 are closely related viruses that belong to the herpesviridae family of DNA viruses (Kupila, Vuorinen et al. 2006). While HSV-1 typically causes encephalitis, HSV-2 is more often associated with aseptic meningitis, and accounts for most cases of Mollaret's syndrome (Workowski 2015). In neonates who acquire infection during delivery through their mother's genital tract, HSV-2 and HSV-1 are equally involved. The highest risk to the neonate is primary maternal infection closest to delivery (Engelberg, Carrell et al. 2003) leading to a high viral load and an absence of specific HSV antibodies in the neonate. On the other side, Mollaret meningitis is characterized by recurrent self-limited lymphocitosis meningitis in otherwise healthy individuals (Tyler 2004). Recurrence takes place at intervals of several weeks to months and has been documented after up to 28 years (Abu Khattab, Al Soub et al. 2009). CSF contains from 200 to several thousand lymphocytes per mm3, and large endothelial cells termed "Mollaret cells" may be present. CSF proteins are elevated and glucose may be low. Complete recovery occurs within several days. Diagnosis is established after other causes of lymphocytic meningitis have been ruled out. The causative agent is HSV-2 (Carmena Carmena, Macia Soler et al. 2004) although other pathogens, HSV-1 included, have also been reported (Sonneville, Klein et al. 2009).

2.2.**Pathogenesis**

The vast majority of viruses enters the CNS via hematogenous spread. In contrast, rabies virus and HSV reach the brain strictly through Trans neuronal spread from a peripheral portal of entry. HSV infects via mucosal surfaces or damaged skin. Primary infections acquired through close contact from an infected individual excreting the virus are mostly asymptomatic or mild in adults and depends on the immunological status of the host, but may result in gingivoestomatitis. After initial replication in the skin and mucosa, the virus infects the sensory nerve endings innervating the infected territory, and migrates by retrograde axonal flow. Thus, latent infection is defined as the presence of the genome of the pathogen in the host tissue without the production of infective particles. The exact pathogenesis of Herpes simplex virus encephalitis (HSE) is unknown and the mechanisms that facilitate HSV-1 ability to penetrate the nervous system, evade the immune response, and cause encephalitis are also not fully understood. Recently, genetic defects have been identified that impair recognition of pathogens by the innate immune system, increasing susceptibility to specific microorganisms. Toll-like receptors (TLRs) are important in the innate immune response. TLR3 is expressed in the CNS, where it may prevent spread of HSV. Two specific immune deficiencies, UNC-93B1 deficiency and mutations in TLR3 can predispose children to HSV encephalitis. UNC-93B is a protein involved in the intracellular trafficking of TLR3 (Zhang, Abel et al. 2013). The outcome of viral infection depends on a subtle balance between the host immune response and viral factors able to counteract it. Widespread local extension and dissemination can occur in patients with inadequate cell-mediated immunity, including infants, organ transplant recipients, and HIV-infected people (Pepose, Hilborne et al. 1984).

The cytokines, interferon, antibodies and the inflammatory cascade, the role of regulatory T cells (CD4+ and CD25+) in encephalitis is receiving particular attention. These cells secrete anti-inflammatory cytokines, including IL-10

and transforming growth factor beta and contribute to limit the response of virus-specific CD8+ in herpes simplex encephalitis, thus limiting the inflammatory and destruction in the CNS.[23] Thereis much interest in the immunological response to the viral infection of the CNS and the clinical importance of it is yet to be determined[26]. These immunological mechanisms are extensively revised in the Libbey and Fujinami review(Libbey and Fujinami2014). Genetics play also a role in the susceptibility to viral encephalitis, particularly to HSE, including mendelian inherited immune defects such as autosomal recessive STAT-1 deficiency, X-linked NEMO deficiency and autosomal dominant TLR3 deficiency(Zhang, Abel et al. 2013).

2.3.**Clinicalfeatures**

The symptoms and signs of HSE are related to nonspecific meningoencephalitis, and include headache, fever and sometimes neck stiffness associated with signs of brain dysfunction (alterations of consciousness, personality behavior, focal neurological signs and cognitive disturbances) and seizures. More specific to HSE are prodromal symptoms of upper respiratory tract infection and neurological findings related to dysfunction of the front temporal lobes, sometimes mimicking acute psychiatric conditions. Fever is one of the most frequent features at presentation, and its absence should cause doubt upon the diagnosis (Barnett, Jacobsen et al. 1994). Later in the clinical course, patients may have diminished comprehension, paraphasic spontaneous speech, impaired memory and loss of emotional control (Hart, Kwentus et al. 1986).

2.4.**Diagnosis**

Early diagnosis is paramount to start therapy as early as possible, which in turn is crucial to obtain a better prognosis.

Electroencephalography (EEG) is almost always abnormal in HSE, showing background slowing and a temporal temporary focus with lateralized epileptiform discharges (PLEDs). PLEDs are unspecific for HSE, they can be found during 2-14 days from the beginning of the disease. EEG has high sensitivity (84%) but low specificity (32%) for the diagnosis of herpes simplex encephalitis (VanLandingham, Marsteller et al. 1988). Brain CT scan results depend on the timing of the exam. Early images (< 48 hours) can be normal or show subtle abnormalities, including white matter temporal lobe hypo density and gyriform enhancement. Delayed imaging (> 4 days) may show signs of bleeding, within areas of brain edema. Almost all patients with proven HSE and a negative initial scan will have abnormalities on a second scan (Steiner, Kennedy et al. 2007). Magnetic resonance imaging (MRI) is significantly more sensitive and specific than CT scan, and is the neuroimaging procedure of choice in patients with suspected HSE. It is much more sensitive in detecting early changes (Hasbun, Abrahams et al. 2001). Typical findings include early diffuse brain edema followed by cortical and sub cortical hypo density or T2W and FLAIR hyper intensities. The temporo-parietal regions and insula are most commonly involved, followed by the frontal lobes and the occipital lobes. Involvement is often bilateral and asymmetrical.

All patients with suspected encephalitis should have a lumbar puncture (LP) as soon as possible, unless there is a clinical contraindication (DeBiasi, Kleinschmidt-DeMasters et al. 2002). The opening pressure is elevated, and CSF can be hemorrhagic. Typically, there is lymphocytic pleocytosis with increased proteins and normal glucose (Tunkel, Glaser et al. 2008). If the first CSF is normal, a second CSF examination after 24-48 hours is likely to be abnormal (Davies, Brown et al. 2005). The gold standard for establishing the diagnosis is the detection of herpes simplex virus DNA in the CSF by PCR. Although PCR may be negative in the first 3 days of the illness, a second CSF taken a few days later will often be positive, even if treatment has been started (Skoldenberg, Aurelius et al. 2006). Viral load declines after treatment in all patients, and prolonged detection correlates with poor outcome. Prior to the availability of PCR testing, brain biopsy was the only way to accurately diagnose herpes encephalitis but nowadays there is no role for brain biopsy in the initial assessment of patients with suspected HSE. It may be useful in patients with suspected

HSE who are PCR negative and deteriorate despite treatment. It may be considered as the last option, when the diagnosis remains unclear (Soong, Watson et al. 1991). The histopathological basis of encephalitis is the association of damage to the parenchyma, reactive gliosis, and inflammatory cellular infiltration. Macroscopically the brain shows necrotic and asymmetrical lesions of the temporal and orbital cortex.

Microscopically, necrosis is associated with diffuse inflammation and peri vascular lymphocytic infiltration. Viral DNA is detectable in brain tissue.

2.5.Treatment

The prognosis of HSE has been transformed by acyclovir therapy. To reduce permanent sequelae, treatment should be introduced as soon as possible and modified according to neuroimaging, serological and PCR results (Whitley and Kimberlin 2005). Acyclovir proved to be the treatment of choice for the reduction of mortality and morbidity from HSE in the 1980's. Acyclovir 10 mg/kg three times a day, improves the outcome in HSE reducing mortality to less than 20-30%. It must be infused slowly and with fluid bolus to prevent crystalluria and renal failure. Duration of treatment in the randomized trials of acyclovir for HSE was 10 days. However, reports of clinical relapse after 10 days treatment were published subsequently, since there was evidence of continuing viral replication in some cases (Valencia, Miles et al. 2004). Consequently, most clinicians use a standard initial intravenous course of 14-21 days of acyclovir that dramatically improves outcomes as measured by the Mental Development Index of the Bayley Scales of Infant Development (Kimberlin, Whitley et al. 2011). Acyclovir should not be stopped on the basis of a single negative CSF PCR, when HSV encephalitis is still suspected clinically. Foscarnet is recommended in acyclovir-resistant HSE (60 mg/Kg intravenously infused over 1h every 8h for 3 weeks). Cidofovir is another second-linedrug.

The role of steroids in the treatment of HSE is not established, since they have inmunosupressor effects, which could facilitateviralreplication. All cases of HSE must be hospitalized and should have access to intensive care unit equipped with mechanical ventilators. Supportive therapy is essential. Seizures are controlled with intravenous anticonvulsants. Careful attention must be paid to the maintenance of respiration, Cardiac rhythm, and fluid balance, prevention of deep vein thrombosis and aspiration pneumonia. Surgical decompression for HSE may be indicated in selected cases for impending herniation or increased intracranial pressure refractory to medical management.

2.6.**Prognosis**

Mortality rates in untreated HSE are around 70% and fewer than 3% would return to normal function. Older patients with poor level of consciousness (Glasgow Coma Scale of 6 or less) had the worst outcome. Sequelae include mostly epileptic seizures, developmental delay, and residual hemiplegia (Raschilas, Wolff et al. 2002).

The disease usually follows a monophasic course, but 12-27% of the patients develop relapsing neurologic symptoms a few weeks after the CSF viral studies become negative and the treatment with acyclovir has been discontinued (Pruss, Holtje et al. 2012). The hypothesis that the disorder is immune-mediated has received strong support by the recent discovery that many of these patients develop immunoglobulin G (IgG) antibodies against the GluN1 subunit of the NMDA receptor (NMDAR) and sometimes to other known and unknown proteins. Anti-NMDA receptor encephalitis is highly predictable in adults and teenagers and usually evolves in stages, including a prodromal phase of fever, headache, or viral-like symptoms that often goes unnoticed. This is followed within few weeks by the onset of psychiatric and behavioral problems including anxiety, bizarre behaviors, that progress to decreased level of consciousness, seizures, choreoathetoid movements and autonomic instability (Hacohen, Deiva et al. 2014). Autonomic dysfunction is also common in adults. In young children the presenting symptoms may be different and are under-recognized. Compared with the brain MRI obtained during HSE (which shows mild or absent contrast enhancement), the MRIs obtained during symptom relapse tend to be abnormal including cortical and sub cortical T2-fluid attenuated inversion recovery signal abnormalities. The diagnosis of the disorder is confirmed by demonstrating

NMDA receptor antibodies in serum and/or CSF. The levels of antibodies in CSF correlate better with symptom outcome than those of serum. Prompt diagnosis is important since a correct therapy can be highly effective showing clinical improvement and dramatic reduction of contrast enhancement in the MRI. Treatment is based on steroids and immunotherapy with or rituximab and cyclophosphamide, alone or in combination.

3.**VARICELLA-ZOSTER VIRUS**

Primary infection with VZV causes varicella (chickenpox) and, once the illness resolves, the virus remains latent in the dorsal root ganglia for a long period of time. The virus can reactivate later, often with advanced age or immune suppression, giving rise to a painful dermatomal rash (shingles). Zoster may be complicated by postherpetic neuralgia as well as meningoencephalitis, myelitis, retinal necrosis, and vasculopathy, including a multifocal VZV vasculopathy with temporal artery infection (Gilden, Cohrs et al. 2009, Nagel and Gilden 2013)

Hematogenous VZV dissemination results in to small- or large-vessel vasculitis. The latter is a granulomatous angiitis that occurs weeks or months after the appearance of zoster vesicles in the first branch of the trigeminal nerve (zoster ophtalmicus) in immune competent and results in ischemic or hemorrhagic stroke. Small-vessel vasculitis appears in immune suppressed subjects without a preceding skin lesion, and causes small ischemic, hemorrhagic, and demyelinating lesions located on the gray-white matter interface of the brain. Finally, periventriculitis in immune suppressed patients may occur as a consequence of ventricular viral dissemination or of ischemic or demyelinating lesions in the per ventricular region, and is often associated to hydrocephalus.

The clinical manifestations in zoster encephalitis are similar to other viral encephalitis. CSF examination shows a mild lymphocytic pleocytosis (around 100 cells per mm^3) with increased proteins and normal glucose. Diagnosis is confirmed by the detection of viral genome in the CSF by PCR or by demonstrating the presence of specific IgM in the CSF or of an increase in the ratio of viral antibodies in the CSF to that in the blood(Gilden, Cohrs et al. 2009). Shingles episodes are often accompanied by asymptomatic CSF pleocytosis, as revealed by lumbar punctures performed for other reasons, and this likely reflect a more frequent CNS involvement than clinically suspected in varicella zoster virus infection.

The incidence of varicella-zoster virus encephalitis is estimated in 1-2 individuals per every 10,000 cases of varicella. The risk of viral reactivation increases with age, immunosuppressive states, and HIV infection (Cohen 2013, Cohen 2013). Despite a lack of randomized therapy trials, the use intravenous acyclovir (10 mg/kg/8 h) is recommended for 14-21 days. When vasculitis is present, steroids are usually added.

4. ENTEROVIRUSES

Enteroviruses (EV) are ubiquitous RNA viruses historically divided among polio virus and non-polio virus. A collective noun used to refer to Coxsackie A and B viruses, Echoviruses and other numbered Enteroviruses (ECDC 2014). Molecular characterization has led to a recent modification into 4 different groups (A-D). They are responsible for 10-20% of encephalitis with a known causative agent, and account for 70-80% of aseptic meningitis. Fecal-oral contact is the usual way of transmission.

Infected patients usually develop flu-like symptoms, although EV can cause a wide spectrum of CNS and PNS disease. EV-71 is known to cause hand, foot and mouth disease, and was also implicated in a large number of fatal cases of encephalitis with a major outbreak in Asia in 1998 (Janes, Minnaar et al. 2014). EV-D68 is recognized to cause a mild-to-severe respiratory illness, and was recently associated with polio-like symptoms, including paralysis and meningo-encephalitis (Messacar, Schreiner et al. 2015).

4.INFLUENZA VIRUS

Influenza is an acute infectious respiratory disease of great public health impact

because of its worldwide distribution and morbidity. Although most influenza complications are pulmonary, extra pulmonary complications can occur.

The neurological complications of influenza virusesincludefebrileseizures, encephalopathy,encephalitis,Reye syndrome, acute disseminated Encephalomyelitis, Guillain-Barre syndrome,post-viralparkinsonism, cerebellitis, andacutenecrotizing encephalitis, among others(Cardenas, Soto-Hernandez et al. 2014). They can occur during infection, where most fatal and severe cases are observed, or after vaccination.

A recent review of 104 articles on the neurological complications after influenza A found encephalopathy-encephalitis as the most common neurological complication of influenza infection, followed by seizures(Cardenas, Soto-Hernandez et al. 2014). Ninety-three percent of patients were children. Five subtypesofinfluenza-associated encephalopathy have been described, and all of them can be associated with seizures:

a) mild encephalopathy with reversible splenial lesion;

b) hemorrhagic shock and encephalopathy syndrome;

c) acute encephalopathy with seizures and late restricted diffusion;

d) acute necrotizing encephalopathy; and e) encephalopathy with malignant brain edema. Seizures are usually generalized tonic-clonic, either single, in clusters or sometimes as status epilepticus.

The pathogenic mechanisms underlying the central nervous system complications of influenza infection are unknown. While pulmonary inflammation is a direct consequence of infection of bronchial and alveolar cells and macrophages, the contribution of viral replication in brain tissues remains unclear. While viral RNA in the CSF has been detected in a few cases, most reported cases lacked CSF pleocytosis, and the viral PCR tested negative, thus suggesting an indirect inflammatory process. It has also been suggested that both vaccination and infection might promote blood-brain barrier dysfunction, resulting in neural tissue inflammation and dysfunction. In this regard, children with an immature blood-brain barrier may be prone to virus invasion due to the size of influenza viral particles(Cardenas, Soto-Hernandez et al. 2014).

5.ARBOVIRUSES

The term *arbovirus* (*ar*thropod-*bo*rne virus) is a descriptive term for viruses transmitted by mosquito and tick vectors. It comprises a group of over 500 RNA viruses of which more than 150 are known to cause disease in humans.

Human infection may go unnoticed or present with highly variable symptoms, including fever, headache, meningitis, encephalitis, and myelitis, sometimes accompanied by flaccid paralysis. Diagnostic is based on blood and CSF serology, essentially ELISA technique for the detection of specific IgM and IgG antibodies. In some cases, PCR analysis is also possible. There is no specific therapy for arbo viruses; however, general measures for prevention, and vaccination when available, are the most effective methods for fighting this infection.

Arboviruses are divided into four taxonomic families: toga viruses (alpha viruses),flaviviridae(flaviviruses), reoviruses, and bunya viruses. Overall, they represent the foremost cause of encephalitis worldwide. Herein we will briefly review the most relevant ones (TABLE 3).

There are more than 150 arboviral pathogens species that get into the CNS through hematogenous spread, leading to transient viremia and seeding in the reticuloendothelial system, muscles and skin where they replicate locally and give rise to secondary viremia and finally reach the CNS via infected T cells, monocytes or endothelial cells of brain capillaries or via an increased in BBB permeability (induction of pro-inflammatory cytokines) or via CSF.

5.1.Toscana virus (Bunya virus)

Toscana virus is a neurotropic arbovirus carried by sand flies (mainly *Phlebotomus)*, first isolated in 1971 (Cusi, Savellini et al.

2010). Human cases of meningitis have been reported in several Mediterranean countries (ECDC 2014). Oftentimes, a benign, aseptic meningitis develops (mostly in young adults) after infection, but encephalitis has also been described. CSF shows lymphocytic pleocytosis, increased protein levels and normal glucose contents.

5.2.West Nile virus *(Flavivirus)*

West Nile virus (WNV) was first detected in Uganda in 1937, but until it reached the Western Hemisphere in 1999 it was considered unimportant as a human pathogen. It has now become the leading cause of arbo viral neuron infection in the United States and is, indeed, widely distributed throughout Europe, Africa and Asia (ECDC 2014). The disease is notifiable at the European Union level (Goldberg, Anderson et al. 2010) (Gubler 2007).

West Nile virus reservoirs are wild birds and mosquitoes (mainly Culex). Occasionally humans are infected through mosquito bites, but, infrequently, infection happens through organ transplantation and blood. Infection peaks arise in the summer, although the overall period extends from May to November.

An incubation period of 2-14 days precedes symptoms, with most human infections being asymptomatic. Around 20% of infected individuals develop a nonspecific flu-like illness known as West Nile fever. One in 150 infected persons discloses important neurologic manifestations as meningitis or encephalitis. Although disease occurs in middle-aged and younger, individuals aged 50 years and older are at higher risk.

Encephalitis is characterized by the appearance of movement disorders, consequence of virus affinity for the basal ganglia. Essentially, it affects sub cortical structures, and therefore aphasia, behavior changes or crisis are infrequent. Acute asymmetric weakness of lower motor neuron type (flaccid tone, reduced or absent reflexes) is also a clinical feature suggestive of West Nile virus infection.

Diagnosis is based on detection of WNV IgM antibodies in CSF. It shows lymphocytic pleocytosis (40% displays polymorph predominance in early stages), moderately increased protein levels (over 100 mg/dl) and normal glucose range. Contrarily to HSV, half the patients with WNV encephalitis initially show normal imaging studies. When abnormalities present, basal ganglia, thalamus, upper brainstem, and cerebellum are involved. If weakness appears, reduced amplitudes of compound motor action potentials (CMAPs) with relatively preserved sensor neural action potentials (SNAPs) are registered on EMG (Li, Loeb et al. 2003).

There is no specific treatment available, and therefore management involves supportive care. At present, there are no vaccines approved for human use but phase I and II clinical trials are ongoing (De Filette, Ulbert et al. 2012).

5.3.Tick-borne encephalitis (Flavivirus)

Tick-borne encephalitis (TBE) is widely spread in Europe, having become a growing public health challenge with an increase by almost 400% in the last 30 years.

The main vectors in Europe are ticks of the family Ixodidae; humans are incidental hosts. Consumption of infected unpasteurized dairy products may also lead to infection. Seasonality shows a clear peak during the summer months, however, tick exposure and bite might occur even during cold seasons (ECDC 2014).

Encephalitis appears after an incubation period of 8 days (4-28 days) following exposure. Disease has a biphasic course and some patients develop a flaccid paralysis with upper extremities predominance.

CSF shows moderate pleocytosis (<100 cells/mm^3) initially with polymorph predominance, later mainly lymphocytic; discreetly increased proteins with normal glucose levels. Neuroimaging may display abnormalities over cerebellum, caudate, thalamus and brainstem and unspecific changes are present in most of the patients. Serum antibodies are usually found on the encephalitic phase of the disease.

There is no specific treatment but effective vaccines are available. TBE

immunoglobulin is no longer used (Bogovic and Strle 2015).

5.4.Chikungunya (Toga virus)

Chikungunya is a viral hemorrhagic fever transmitted by Aedes mosquitoes to vertebrates. It was first isolated in India in 1963 with several outbreaks since then (Higgs and Vanlandingham 2015). Recently indigenous cases have been reported in Europe but usually infection is travel-related (ECDC 2014).

The most common clinical form associates fever, rash and strong arthralgia, however meningoencephalitis with myeloradiculitis has been described (Ganesan, Diwan et al. 2008). Recovery is the usual outcome. Diagnostic tests are available but there is no antiviral or licensed vaccine.

5.5 ZIKA VIRUS

The Zika virus is an arthropod-borne virus (*arbovirus*) belonging to the *Flavivirus* genus. It was first isolated in the Zika Forest of Uganda in 1947 from rhesus monkeys and reported in humans in 1954(Garcia E 2016). Like dengue fever, Zika is transmitted by mosquitoes in the genus *Aedes*, which are widely distributed in subtropical and tropical areas of the world. The evidence of sexual transmission is also cause of concern (Musso, Roche et al. 2015, Atkinson, Hearn et al. 2016). The infection remained endemic for years in a narrow belt from Africa to Asia, but it expanded dramatically in the last decade across the Pacific Ocean to America, reaching worrisome levels in 2016 (Garcia E 2016).

Until know, Zika infection was considered a mild dengue-like disease, causing fever, muscle pain, rash, and headache. Currently, its importance has increased due to the evidence of associated microcephaly and other fetal malformations among fetuses of pregnant women infected by the Zika in Brazil in 2015 and later(Heymann, Hodgson et al. 2016, Mlakar, Korva et al. 2016, Rasmussen, Jamieson et al. 2016).

The presumptive neurological involvement of this virus is also reflected by its association with peripheral neuropathies, in particular cases of Guillain-Barre Syndrome (GBS). Although the precise mechanism is unknown, hypotheses include the direct effect of Zika virus against peripheral nerves and molecular mimicry between nerve components and viral antigens. The first cases of GBS related to Zika virus were described in French Polynesia in 2013(Cao-Lormeau, Blake et al. 2016) and, recently, multiple cases of GBS have been documented in Brazil, Venezuela and other South American countries. Indeed, a case of a Haitian male with a GBS-variant (Miller Fisher syndrome) was reported in January 2016(Kassavetis, Joseph et al. 2016).

Involvement of the CNS has also been reported recently, including a 81-year old male affected by meningoencephalitis in the context of an infection with the Zika virus(Carteaux, Maquart et al. 2016), and two cases of acute disseminated encephalomyelitis following a Zika infection(Ferreira 2016).

Diagnostic work-up includes reverse transcription polymerase chain reaction (RT- PCR) analysis, confirming the presence of virus RNA or antigen in serum or other samples (e.g., cerebrospinal fluid), and the presence of IgM against the virus. Serological studies, however, should be interpreted with caution, as they are subject to cross reactivity with other Flavivirus(Organization 2016).

Prevention of this infection (use of insect repellent, screen and nets, and avoid stagnant water) is of utmost importance, since there is yet no specific treatment available and vaccines are not available. Management is supportive.

6. TREATMENT OF ACUTE ENCEPHALITIS IN ADULTS.

For most CNS viral infections no specific therapies are available. However, it is extremely important to institute an early specific treatment whenever possible, and it is also essential to provide supportive therapy in all cases. Patients with encephalitis should ideally be treated in intensive care units in order to receive a careful attention, because of the potential complications that include respiratory and

circulatory problems, increased intracranial pressure, and secondary infections, among others.

6.1. General management

The initial priority is to ensure patient´s safety, and the ABC (airway-breathing-circulation) is an essential approach(Venkatesan and Geocadin 2014). The first step is to provide a permeable airway and adequate oxygenation. Patients may develop respiratory insufficiency, usually due to airway collapse secondary to decreased level of consciousness, to aspiration and, less commonly, to neurogenic pulmonary edema.

In some cases (i.e., encephalitis caused by Flavivirus) a flaccid paralysis could also result in respiratory failure(Garcia-Monco 2010). Endotracheal intubation and mechanical ventilation may therefore be needed in some instances. Ensuring brain perfusion and hemodynamic stability is also critical, since autonomic dysfunction may be present; it is particularly common in non-infectious, autoimmune encephalitis against the NMDA receptor (Venkatesan and Geocadin 2014).

Seizure management is also important. Indeed**,** status epilepticus in critically ill patients with encephalitis is present in 15% of patients (Abend, Bearden et al. 2014), and non-convulsive status can be the initial presentation. The electroencephalogram (EEG) is of particular importance, especially in patients with fluctuations in the level of consciousness, to determine whether these changes are the result of the encephalitis or are secondary to epileptic seizures. Moreover, many patients may present periodic lateralized epileptiform discharges (PLEDs), without evident clinical manifestations. Therefore, continuous EEG monitoring if available would be optimal to improve diagnosis and to control effectiveness of antiepileptic drugs (AEDs) .The goal of treatment is to control epileptic activity (using short-acting intravenous agents such as lorazepam/diazepam or midazolam) followed by or long-acting AEDs (i.e., phenytoin, levetiracetam, or valproic acid). In particular cases, refractory seizures will require a more aggressive approach with barbiturates, propofol, or ketamine to induce a burst-suppression pattern on EEG (Kramer and Bleck 2008, Venkatesan and Geocadin 2014)

The presence of raised intracranial pressure (ICP) should be suspected in patients with decreased level of consciousness, vomiting, or persistent headache and treated properly after neurosurgical consultation. Neuroimaging should be performed urgently and systemic conditions aggravating the ICP (i.e., fever, hypoglycemia) corrected. The main goal of treatment is to avoid brain herniation that can lead to permanent brainstem injury. General measures should include elevation of the head of the bed 30º, correcting hypoxemia, hypercapnia and agitation. If mass effect is important, hyperosmolar therapy with the use of mannitol solution 20% (0.25 to 1 g/kg) boluses every 4– 6 hours IV) or hypertonic saline (2-3% peripheral vs. central line) is recommended. In the setting of hyponatremia, mannitol is preferred, because of the potential risk of osmotic demyelinization syndrome with a rapid correction with saline (Kramer and Bleck 2008, Venkatesan and Geocadin 2014). Decompressive craniectomy or entriculostomy to alleviate ICP may be necessary if there is progressive worsening. Although it has been described that early surgical decompression could improve neurological outcome(Yan 2002) , randomized controlled trials are now underway to determine whether it really improves long-term outcomes (based on Decompressive craniectomy used to control refractory ICP in patients with trauma brain injury)(Kramer and Bleck 2008).

6.2. Specific treatment

Ascertaining a specific etiology takes days or even weeks, and is possible in a small percentage of patients. Therefore, it is crucial to initiate empiric therapy for the most common etiology of sporadic encephalitis (Herpes simplex virus-1) as soon as a clinical suspicion of acute encephalitis is present. Details about its administration are described in the corresponding section of this chapter.

In Varicella Zoster Virus (VZV) encephalitis, acyclovir (same doses as HSV during 21 days) is also the mainstay of therapy, and there is stronger evidence for steroid therapy, because of the potential presence of vasculitis (granulomatous angiitis) following the infection. The duration of steroid treatment should be short (between 3 and 5 days) to minimize adverse effects (Steiner, Budka et al. 2010).

In patients with cytomegalovirus encephalitis intravenous ganciclovir (5 mg /12 h for 2 weeks) followed by a maintenance dose of 5 mg / kg / day is required. Some authors recommend associating foscarnet (60 mg/kg every 8 h)(Steiner, Budka et al. 2010). Treatment recommendation for HHV6 encephalitis is foscarnet (60 mg/kg every 8 h) (Steiner, Budka et al. 2010)

Among other encephalitic etiologies, autoimmune and paraneoplastic etiologies should not be forgotten, and clinicians should be aware of recent advances in its management. The approach will vary depending on the severity of the encephalitis and the underlying neoplasm, if it is present. First line treatments include corticosteroids (IV metylprednisolone, 1000 mg daily for 5 days), IV immunoglobulin (typically 0, 4 g/kg for 5 days), and plasmapheresis either alone or in combination. Second-line treatments consists of cyclophosphamide and rituximab(Venkatesan and Geocadin 2014). In the case of paraneoplastic syndromes, resection of the tumor (i.e., teratoma in NMDAR encephalitis) and specific antineoplastic treatment are often necessary.

In summary, a high index of suspicion of encephalitis should be kept in patients with fever and neurological abnormalities so that proper diagnostic and management measures are immediately taken, including urgent neuroimaging and cerebrospinal fluid analysis.

The treatment of encephalitis patients requires a multidisciplinary approach, often in the Intensive Care Unit, and includes the use of specific drugs in certain circumstances (e.g., acyclovir in herpes simplex encephalitis), as well as measures for the general control of the patient and for the management of associated features such as concomitant infections and drug-related adverse events. All these measures together have resulted in a clear improvement in the prognosis of patients with viral encephalitis.

Table 1. Most common etiology of acute encephalitis	
Etiologic agent	Comments
Herpes simples	All year
Enterovirus	Summer and fall
Arbo virus	Summer and fall Transmitted by mosquitoes or ticks

Table 2. Suspected etiological agent depending on associated neurologic symptoms	
Clinical manifestation	Suspected virus
Ataxia	VVZ (children), EBV, mumps, San Luis encephalitis
Parkinsonism	San Luis encephalitis, Japanese encephalitis, WNV
Cranial nerve palsy	HSV, EBV
Dementia	VIH
Polio-like flaccid paralysis	WNV, Japanese encephalitis, tick-borne encephalitis, Enterovirus (EV-71, EV-D68, Coxackie, poliovirus)
Rhomb encephalitis	HSV, WNV, EV-71
VVZ: Varicella-zoster virus; EBV: Epstein Barr virus; HSV: Herpes simples virus; WNV: West Nile virus	

Table 3. Main arbovirus capable of neurologic disease in humans					
	First isolated	Distribution	Vector	Host	Disease
Flavivirus					
Tick-borne encephalitis	Russia, 1937	Europe, Asia	Ticks (*Ixodes spp.*)	Rodents	Encephalitis, flaccid paralysis
West Nile virus	Uganda, 1937	Worldwide	Mosquitoes, ticks	Birds	Encephalitis,flaccid paralysis
Japanese encephalitis	Japan, 1935	Asia	Mosquitoes (*Culex*)	Birds	Encephalitis
San Louis encephalitis	EEUU, 1933	Central and South America	Mosquitoes (*Culex*)	Birds	Encephalitis
Dengue	New Guinea Philippines, Hawaii, 1944	Tropical and sub-tropical areas	Mosquitoes (*Aedes aegypti*)	Humans	Fever and exanthema
Yellow fever	Ghana, 1927	Sub-Saharan Africa South America	Mosquitoes (*Aedes spp.*)	Apes	Jaundice
Bunya virus					
Toscana virus	Toscana, Italy 1971	Mediterranean bay	Mosquitoes (*Phlebotomus spp.*)	Unknown	Aseptic meningitis
Toga virus					
Western equine encephalitis	EEUU, 1930	EEUU	Mosquitoes (*Culex and other species)*	Birds and rabbits	Encephalitis
Eastern equine encephalitis	Massachusetts, 1981	America	Mosquitoes (*different species)*	Birds	Encephalitis (enduring pleocytosis in CSF)
Venezuelan equine encephalitis	Venezuela, 1938	Central and South America	Mosquitoes (*different species)*	Rodents	Encephalitis
Chikungunya	Tanzania, 1956	Africa, Indian Ocean basin	Mosquitoes (*Aedes spp.*)	Apes	Hemorrhagic fever

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