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Research Article

An Update on Aetiopathogenesis and Management of Japanese Encephalitis - A Systematic Review

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Abstract

A systematic review was carried out regarding the aetiopathogenesis of Japanese encephalitis along with its management using the pubmed search engine for MeSH terms like Japanese encephalitis, Japanese encephalitis virus; epidemiology; treatment ;vaccines for this systematic review from 1955 till date in 2020. We found a total of 6817 articles out of which we selected 50 articles for this systematic review. No meta-analysis was done. JEV and West Nile virus (WNV) are the most common encephalitic Flaviviruses. The family of Flaviviridae contains >70 members which were initially separated on the basis of cross reactivity of the antibodies they induce. Initial evaluations with polyclonal antisera into 7 subgroups, known as serocomplexes. Members of the same serocomplex are defined by the cross neutralization of the antibodies they induce. JEV and WNV belong to the same JEV serocomplex in combination with other viruses like Murray Valley encephalitic virus (MVEV), St Louis encephalitic virus (SLEV), as well as Usutu virus (USUV). Both JEV and WNV share certain ecological similarities since they maintain an enzootic transmission cycle with various bird families as natural reservoirs and mosquitoes of the Culex species as main vectors. Nonspecific treatment is available till date despite the global importance and severity of presentation causing mortality or lot of life long sequelae. Here we have tried to detail how to manage a case of acute encephalitis having a differential diagnosis of Japanese encephalitis once out of the critical stage. Role of innovative drugs that are investigational as well as orlistat is elaborated as well as different vaccines and cross reactivity of JEV antibodies with Zika virus, WNV as well as cost effectiveness of JE vaccine.

Keywords: Flaviviruses; Japanese Encephalitis; JEV; Acute Encephalitis; MRI; Orlistat

Introduction

Japanese encephalitis is a mosquito-borne disease which takes place in Asia and is caused by Japanese encephalitis virus (JEV), a member of the genus Flavivirus. Though many Flavivir used might cause encephalitis, JEV leads to severe neurological manifestations. The virus causes loss of >disability adjusted years than any other arthropod borne virus in view of the common neurological complications of this condition. In spite of marked advances in our advances in getting insight into Japanese encephalitis via *in vitro* studies carried out in animal models, studies of pathogenesis as well as therapy in humans are much behind. Very few studies explaining the mode have been carried out in humans, with only 4 clinical trials of therapies for Japanese encephalitis have occurred in the last decade in spite of a calculated incidence of 69,000 cases/year. Earlier trials for Japanese encephalitis may have been very small for getting the essential advantages of potential therapies. A lot of potential therapy targets are present for Japanese encephalitis, with pathogenesis as well as virological studies having uncovered mechanisms via which these drugs might work. Hence Turtle and Solomon summarized the epidemiology, clinical features, prevention as well as therapy of Japanese encephalitis and concentrated on potential new therapeutic methods, depending on the repurposing existing compounds which are already suitable for human use and could be trialled without delay. Thus they hypothesized potential new treatments, detailing some of the different challenges that still continue regarding therapy of diseases in humans [1].

Methods

We searched the pubmed engine for MeSH terms like Japanese encephalitis, Japanese encephalitis virus; epidemiology; treatment ;vaccines for this systematic review from 1955 till date in 2020.

Results and Discussion

We found a total of 6817 articles out of which we selected 50 articles for this systematic review. No meta-analysis was done.

Details of JEV structure, epidemiology and prevalence in domestic birds

JEV and West Nile virus (WNV) are the most common encephalitic Flaviviruses. The family of Flaviviraede contains>70members which were initially separated on the basis of cross reactivity of the antibodies they induce. Initial evaluations with polyclonal antisera into 7 subgroups, known as serocomplexes [2]. Members of the same serocomplex are defined by the cross neutralization of the antibodies they induce. JEV and WNV belong to the same JEV serocomplex in combination with other viruses like Murray Valley encephalitic virus (MVEV), St Louis encephalitic virus (SLEV), as well as Usutu virus (USUV).

Both JEV and WNV share certain ecological similarities since they maintain an enzootic transmission cycle with various bird families as natural reservoirs and mosquitoes of the Culex species as main vectors [3,4]. Humans as well as horses are thought to be dead end hosts, since they don't develop a viremia high enough for infecting Mosquitoes. The exception is pig, since they serve as amplification hosts for JEV since they form enough viral titres for supporting further infection of mosquitoes [5]. Though the part of ardeid birds as reservoir hosts for JEV is admitted [6], role of domestic birds as potential amplification hosts has been little evaluated thus far. Various surveys implemented in separate continents point to the involvement of domestic birds, mainly ducks, in WNV epidemiological cycle, either as an amplification hosts or in the form of a reservoir hosts [7]. For JEV, 2 experimental studies point that young birds, mainly ducks might produce enough viremia to infect Mosquitoes when biting [8]. In view of their close association with humans, as well as differing amount of seroprevalence seen in domestic birds, their part in epidemiological cycle as secondary reservoirs might be essential [9].

JEV is mostly found across Eastern, Southern, and South eastern Asia where it is the most commonly isolated pathogen for encephalitis in humans [10]. In spite of the availability of various vaccines since the 1990's, Japanese encephalitis is still a clinically important disease with roughly 70,000 cases/yr,=>10, -15,000 deaths [11,12] and leaves ~30-50% survivors with definitive neurological or psychiatric complications [4].

The basic aim of the study by Auerwald., et al. was to find the prevalence of JEV and WNV Flaviviruses. In domestic birds, elaborated in chickens as well as ducks in 3 various Cambodian provinces. They found the Flavivirus seroprevalence utilizing a haemagglutination inhibition assay (HIA). Further in positive samples they evaluated the presence of JEV and WNV neutralizing antibodies (nAb) utilizing the foci reduction neutralization tests (FRNT). They observed 29% (180/620) of the evaluated positive for Flavivirus antibodies with an age based escalation of seroprevalence (OR = 1.04) and a >prevalence in ducks as compared to chickens (OR = 3.01). Within the Flavivirus positive birds, they found 43% (28/65) with nAb against JEV. They also saw the anticipated cross reactivity between JEV and WNV, by finding 18. 5% double positive birds that had > titers of nAb against JEV. Moreover 7 domestic birds, (10.7%) demonstrated only nAb against JEV. Thus their study gave proof of a marked JEV circulation in domestic birds in Cambodia, and the 1st serological proof for WNV presence in South eastern Asia since decades. These findings point the requirement of a redefinition of areas at risk for JEV and WNV transmission, and our need for more intensive surveillance of Mosquitoes transmitted diseases in domestic animals [13].

Case reports of Japanese encephalitis

Citing a case report by Keng and Chang [14] of a 52yr old man admitted with fever, headache as well as drowsiness of one day's duration. He had neck stiffness and equivocal Kernig and Brudzinski signs. Cerebrospinal fluid (CSF) demonstrated increased protein level, normal glucose concentration and lymphocytic pleocytosis. The patients mental status worsened on day 4. He became comatose, needing mechanical ventilation. No Intra Cranial Haemorrhage was found on CT Scan. Serial MRI with fluid attenuated inversion recovery sequence (figure 1A, on day 1, and 1B on day 5) revealed continuously lot of high signal intensities in the bilateral thalami (arrows) in the bilateral thalami caudate nuclei and internal capsules. Diffusion weighted MRI illustrated hyperintensity in the same area. No proof of occlusion or high grade stenosis of the basilar artery as well as main trunk of the bilateral post cerebral arteries. The finding was suggestive of Japanese encephalitis, with the diagnosis corroborated later when the virus was found in the CSF by real time reverse transcriptase polymerase chain reaction (PCR). In spite of aggressive therapy with intravenous immunoglobulin as well as high dose intravenous steroids, patient died 30 days following admission.

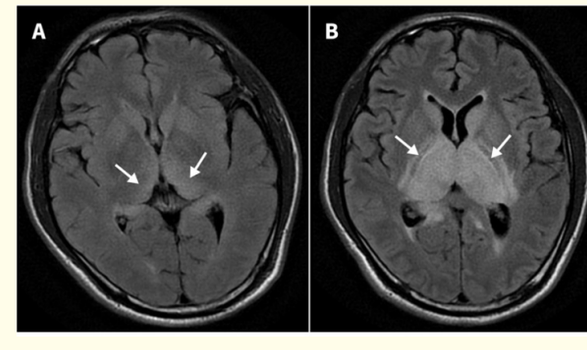

Figure 1: Courtesy ref no-19- (A) Brain magnetic resonance imaging (MRI) scan with fluid-attenuated inversion recovery (FLAIR) sequence on day 1 showing mildly high signal intensities in the bilateral thalami (arrows) in a 52-year-old man with Japanese encephalitis. (B) Brain MRI with FLAIR sequence on day 5 showing markedly high signal intensities in the bilateral thalami (arrows), caudate nuclei and internal capsules.

JEV, is the most common cause of viral encephalitis in Asia as well as western Pacific rim. Though most of those infected are asymptomatic, 20 - 30% of those who present with overt disease have fatalities with 30 - 50% of survivors of those surviving having neurologic, cognitive or behavioural complications [15]. Clinical Features are acute febrile illness, changed mental status, acute psychosis, seizure and acute flaccid paralysis. Thalamic abnormalities viewed on imaging, like hypodensity on computed tomography (CT) and hyper intensity on T2 -weighted, magnetic resonance imaging (MRI), have a specificity for Japanese encephalitis in endemic areas [16]. Despite MRI having>sensitivity as compared to CT in finding Thalamic lesions in Japanese encephalitis [17], its diagnostic utility remains unclear. Due to slowness of diagnosis, mean duration documented between onset and MRI is roughly 10 - 20 days [16,17]. The Differential Diagnosis are metabolic diseases (like hypoxic-ischemic encephalopathy, Wilson disease or Wernicke encephalopathy), vascular diseases (Deep cerebral thrombosis or arterial occlusion), neoplasms s (like primary thalamic glioma) and flavivirus encephalitis different from Japanese encephalitis (like West Nilefever and Murray Valleyfever [18]. Therapy of Japanese encephalitis remains supportive with no efficacious therapy [19].

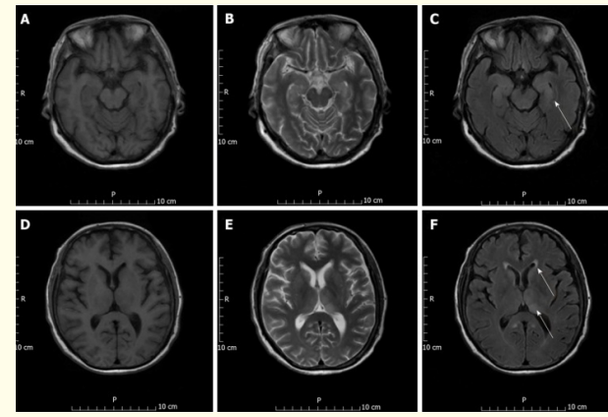

Figure 2: Courtesy ref no-20-Enhanced magnetic resonance imaging scan of the patient's brain on post-transplantation day 19. A, B, D, E: Lesions can be seen in T1 image (A, D) and T2 image (B, E) ; C: Hyperintense lesion is seen in this T2 fluid attenuated inversion recovery image in parahippocampal gyrus; F: Hyperintense lesions are seen in this T2 fluid attenuated inversion recovery image in the bilateral thalamus and caudate nucleus. Arrows indicate the lesions.

Another case was reported by Qi., *et al.* [20] of a woman who underwent liver transplantation for autoimmune liver disease but presented with fever and neurological symptoms 13d after transplantation. Magnetic resonance imaging revealed JEV infection, and positive immunoglobulin M antibody to JEV in blood and cerebrospinal fluid confirmed JE (Figure 2). The patient was treated with antiviral agents, immune regulation, and organ function support. No neurological sequelae were present after 1 year of follow-up. Thus they concluded that Imaging and lumbar puncture examination should be performed as soon as possible in patients with fever and central nervous system symptoms after liver transplantation, and the possibility of atypical infection should be considered, which is helpful for early diagnosis and improved prognosis [20].

Management of Acute encephalitis in general as presentation is very severe

Reviewing the management of Acute encephalitis, Kumar [21] pointed that causes are variable including viral and nonviral infections of the brain along with autoimmune processes. In the West now autoimmune encephalitides are now more common than any single infectious cause but in Asia, infectious causes still comprise >aetiologies of AE. In 2006, the WHO brought the term "Acute encephalitis syndrome (AES)" that just means acute onset of fever with convulsions and changes in consciousness or both. In 2013, the International Encephalitis Consortium brought out criteria for encephalitis diagnosis on the basis of clinical and laboratory parameters. The most important infectious causes in the West is herpes simplex Virus but globally Japanese encephalitis remains the single largest cause. Etiologic diagnosis is difficult due to a large Number of agents that can cause encephalitis. Further the responsible virus might be found in brain only and is either absent or transiently found in blood or CSF. Virological diagnosis is complex, expensive and time consuming. Various centres might make their own algorithms for investigation in accordance with the scene in their local area. MRI and electroencephalogram (EEG) are specific for few agents. Clinical severity might differ widely. A severe case might manifest with fever, convulsions, coma, neurologic deficits, and death.

Autoimmune encephalitis (AIE) comprises of 2 main group) classic paraneoplastic limbic encephalitis (LE) with autoantibodies against intracellular neuronal antigens (e.g. Hu and Ma2) and ii) new type AIE with autoantibodies to neuronal surface or synaptic antigens (e.g. -anti-N-methyl-D-aspartate receptor). AIE has prominent psychiatric manifestations: psychosis, aggression, mutism, memory loss, euphoria, or fear. Seizures, cognitive decline, coma, as well as abnormal movements are common. Symptoms might fluctuate rapidly.

Treatment is mainly supportive. Specific therapy is available for herpes simplex virus group and nonviral infections. Different forms of immunotherapy are utilized for AIE.

A severe case needs to be looked after in intensive care unit (ICU). An active search for treatable cause of AES should persist in addition to other methods for protection of the brain through more insult.

Management is supportive as well as specific

Supportive therapy

- Airways, breathing as well as circulation needs to be maintained. Body temperature has to be got down utilizing proper antipyretics. Hydration, electrolyte status as well as acid-base parameters need to be kept within normal limits. Proper antibiotics need to be used till a bacterial cause is ruled out for sure.
- Convulsions need to be treated best by Intravenous anticonvulsants like phenytoin or valproate that do not depress the sensorium. Tube feeding might be initiated on stabilization of patient and control of convulsions. Care is required for avoiding aspiration, and protocol for a comatose patient needs to be followed. Patient needs to be placed in a lateral or semi prone position.
- If there are signs of intracranial pressure (ICP), mannitol infusion (0.25 to 1.0 mg/kg every 4 - 6hrs) or Intravenous furosemide might be required. Hypertonic saline (3%) in a dose of 0.1 to 1 ml/kg/hr for maintaining serum sodium between 145 - 155 mEq/L is another way. Hyperventilation to keep arterial CO_2 tension between 25 and 30 mm Hg might also be used for tackling raised intracranial tension (ICT). If facilities are there, monitoring of ICT is useful. If there is fast increase of ICT with clinical deterioration unresponsive to medical therapy, surgical decompression might be life saving.
- Gastric haemorrhage (stress ulcer) is a common occurrence and needs to be managed with antihistamines, antacids, ranitidine and if required a blood transfusion.
- The role of steroids in Acute infectious encephalitis is debatable. Theoretical arguments for and against their use. Conversely, life threatening increase in ICT might get relieved by steroids, but on the other hand, a risk of flare of viral infection with steroids remains. A study examining high dose dexamethasone in JE detected no advantage of steroid therapy [22].

Typical MRI in JE causes T2 hyperintensities in thalami, basal ganglia and brain stem. Temporal lobe changes are seen in a small proportion of JE also (reviewed in 21). EEG needs to be looked for encephalopathy, localizing signs, or subclinical seizure activity. In case of HSVE characteristic patterns like periodic localizing epileptiform discharges -seen in 1/3rd of cases.

Specific therapy

Of the viral agents specific therapy is recommended in encephalitis due to herpes simplex group of viruses. Acyclovir in a dose 10mg/kg given as an Intravenous infusion over 1hr every 8hrs for 14 days (21 days in immunocompromised cases) is needed in herpes simplex viral encephalitis HSVE [23]. The success of anti-viral therapy is based on early initiation of therapy. In many centres in West, in the lack of an epidemic, Acyclovir is initiated as soon as viral encephalitis (VE) is suspected clinically, irrespective of presence of any localization. In the case of India no hard criteria can be laid down as the relative importance of HSVE in various areas of the country in unknown. It appears reasonable to initiate Acyclovir in non seasonal cases, particularly if focal features are there or neuroimaging studies show temporal lobe involvement. The toxicity as well as adverse actions of Acyclovir are bone marrow suppression, vomiting as well as hypotension following Intravenous infusion, and rarely nonoliguric renal failure in dehydrated patients. Confusion, hallucinations, seizures and coma are rare. Blood counts as well as relevant biochemical tests need to be closely watched. In the presence of renal involvement one needs to be careful since 80% of the drug gets excreted unchanged in the urine. Relapses might occur as > 5%of cases. Resistance to Acyclovir is rare (roughly 0.5% of immunocompetent patients [24]. Foscarnet is utilized in Acyclovir - resistant HSE [23]. Acyclovir is also recommended for varicell-zoster encephalitis, and ganciclovir is an alternative drug. Combination of ganciclovir as well as Foscarnet is recommended for cytomegalo virus (CMV) encephalitis.

Pleonaril is a drug that is under investigation for enteroviral infections, that works by inhibition of viral attachment as well as uncoating [25] Oseltamivir might be considered in case of influenza (HIN1) encephalitis/encephalopathy [25]. Trials with interferon α as well as nasogastric ribavirin in JE in children have showed no benefit [26,27]. The tetracycline drug minocycline is a known neuroprotective agent having antiviral properties as well as excellent penetration into CSF. A trial of naso gastric minocycline in AES in Lucknow showed modest advantages in both cumulative mortality at 3mths from onset as well as neurologic complications. Intravenous azithromycin or oral minocycline/doxycycline is currently recommended for ricketssial meningoencephalitis. Therapy of AIE is immunosuppression via high dose methyl prednisolone pulse therapy, Intravenous immunoglobulin, plasmapheresis, rituximab, and azathioprine.

Role of newer therapies

Although millions of population worldwide are infected by JEV, with incidence escalating year by year right now no specific drugs are there for its therapy. But vaccines are available for its prevention but not efficacious against all clinical isolates. Hence urgent requirement for new chemical entities or exploring molecules that exist for therapy. Thus VN., *et al.* used virtual ligand screening (VLS) method for screening out selected phytoconstituents of genus *Arisaema* against different targets (NS5, NS3 helicase, and NS2B-NS3 protease) of JEVs that exhibit key role in replication,

infection cycle as well as host interactions by using molecular docking and then molecular dynamics (MD) simulations. Screened natural chemical entities showed good binding affinity along with optimum stability towards NS5 as well as NS3 helicase. Moreover the drug likeness analyzed by Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) analysis was detected to be in the acceptable range. Thus concluding, that these natural entities might be thought to be promising candidates regarding formation of anti- JEV drugs. But more investigations are needed to confirm their precise role in JEV infection via *in vitro* as well as *in vivo* experiments [28].

A recent search has found chymase, a mast cell specific protease as an exclusive innovative therapy target for prevention of JEV induced Japanese encephalitis. Intriguingly JEV stimulates mast cell specific chymase at the time of its penetration via blood brain barrier (BBB) that ultimately guide to viral encephalitis. Thus in this study by Kant., *et al.* natural chemical entities (NCE) via multiple databases (MPD3, TIPDB and MTDP) were virtually screened for their binding affinity as chymase inhibitors, a promising negotiator for long surviving against JEV stimulated encephalitis. Merged computational programs, Maestro software, Qik Prop, Protox and Gromacs were applied to screen the NCE's against target receptor (PDB: 4KPO). Three hits (C00008437, C00014417 and 8141903) were found after using a series of sieves like High throughput virtual screening (HTVS), Standard precision (SP) and Xtra precision (XP) molecular docking simulations followed by wanted pharmacokinetic -toxicity profile predictions as well as molecular docking (MD) examinations. Maestro simulations lead to best 3 binding energy scores as -11.992 kcal/mol (1st ranked; C00008437), -11. 673KCAL/MOL (2ND rankedC00014417) and -11.456 kcal/mol (3rd ranked; kcal/mol (1st ranked;), respectively. The top 3 hits showed an ideal range of pharmacokinetic and toxicity descriptors values. Additionally MD simulations aided the authors to confirm top hits higher selectivity towards chymase receptor. They concluded, this may potentially represent innovative classes having an efficacious chymase mediated therapy for combating JEV stimulated encephalitis, that needs to be proved with more detail studies [29].

Role of orlistat

Mosquito transmitted viruses are significant public health problem in a lot of tropical as well as sub tropical countries, with some of the maximum significant human pathogens belonging to the genera Flavivirus and Alpa virus [30]. The genus Flavivirus consists of 53 virus species [31] of which >50% get transmitted by mosquitoes with most having the potential to infect humans [32]. Medically important mosquito transmitted virus in the genus Flavivirus are dengue virus (DENV), JEV, Zika virus (ZIKV) as well as a yellow fever virus (YFV). The genus Alpa virus comprises of 31 virus species [33], with most get transmitted by mosquitoes as well as medically important alphaviruses that include chikungunya virus (CHIKV), Ross river virus, as well as Sindbis virus [34].

Viruses in both genera are enveloped viruses. At the time of viral replication, the newly developed genomic RNA is packaged together along with capsid proteins that is then enveloped in a host derived lipid bilayer in which the viral structure envelope proteins are embedded [33]. Due to this step, host derived lipid makes up an estimated 17% of the Flavivirus as well as a30% of the Alpa virus virion total weight [34].

Various studies, especially those done in case of Flavivirus have clearly revealed that needs of host cell lipid metabolism for viral replication as well as assembly and right now it is thought that Flavivirus remodel host cell metabolism to aid their own replication [35]. Lipid modeling has been posited to promote escalated β-oxidation for giving energy for replication [37] along with changes in membrane fluidity for aiding in right assembly of the virion [38]. Additionally, lipid droplets have been posited to be necessary for proper encapsulation of the nucleocapsid [31]. The probable multistep need for host cell lipids at the time of viral replication points that these processes become good targets for formatting anti viral drug formation.

Orlistat (tetra hydrolipstatin), a United States Food and Drug Administration (USFDA) approved drug inhibits the thio esterase domain of (fatty acid synthase [FASN]), a crucial enzyme needed for denovo synthesis of long chain fatty acids (LCFA) [39]. This drug has been used for weight loss and acts via inhibition of pancreatic lipase, causing reduced absorption of fats via diet, and thus escalation of secretion of fats in stool [40,41]. Since >amounts of fatty acids (FA's) from lipid biosynthesis can help in fast growth acids replication of cancer cells, Orlistat has also been analyzed for its use for treatment of a lot of cancers that include endometrial, prostate, breast acids colorectal cancers [42-45]. Orlistat has also been analyzed as an antiviral agent, with earlier studies showing use in coxsackie virus B3 acids varicella zoster virus [34]. Hitakarun., *et al.* tried to evaluate the broad utilization of Orlistat in decreasing virus infection for variety of Flavivirus (DENV; 9 isolates evaluated), (JEV, 1 isolate examined) acids (ZIKV;2 isolate examined) along with Alpa virus (CHIKV; 2 isolate examined). 3 varying therapy regimens were examined, i.e. level of infection pretreatment (only), post treatment (only), as well as pre as well as post treatment and 3 parameters analyzed i.e. level of infection, virus titre as well as genome copy number. Results revealed that all 3 treatment regimens were capable of significantly decreasing virus titres for all viruses analyzed, other than 3 isolates of DENV in the pretreatment (only regimens. Pre as well as posttreatmen had >effectiveness in decreasing the level of infection as well as genome copy number of all the viruses analyzed than either pretreatment

or post treatment alone. Together these results point that Orlistat has a potential as a wide spectrum agent against lot of mosquito transmitted viruses [46].

Role of vaccines

Currently Zika virus (ZIKV) has become spread at a >pace and hence caught eyes of researchers globally. The vaccine against JEV is used in China at present, as included in planned immunisation regimes. Though ZIKV and JEV are closely associated mosquito -borne Flaviviruses, and a complicated cross-immune response within Flaviviruses has been shown, the action of JEV Vaccination on ZIKV infection has not been detailed. Hence, the study by He., et al. had the objective to evaluate the effect of various titres of anti -JEV antibodies (Abs) against ZIKV infection utilizing sera from healthy human donors in Guangzhou and anti- JEV rabbit polyclonal antibodies (p Abs) *in vitro* and *in vivo*. Human anti- JEV Ab titres were examined at reducing amounts as age escalated. A neutralizing action on ZIKV infection was seen when anti- JEV Ab titres in human sera or rabbit p Abs were raised (the corresponding age being <e30yrs). Despite a <titre in human sera displayed no visible action, while rabbit p Abs displayed an antibody-dependent enhancement (ADE) action, with them showing an ADE action *in vivo* first time. Their study pointed that persons >60yrs of age are at a risk for ZIKV and JEV infection, as well as screening this age group for infection would help. Moreover, a deep evaluation of the association among anti- JEV Ab titres as well as ZIKV infection is required [47].

Studies evaluating West Nile virus (WNV) NS4B Protein function get hampered by the absence of an antibody that recognise WNV NS4B Protein. Minimal laboratories s have developed WNV NS4B antibodies, out of which no antibodies work consistently. Hence Kaufusi., *et al.* described a NS4B Antibody towards JEV NS4B Protein which cross reacted with the NS4B Protein of WNV but not of DENV. This JEV NS4B Antibody besides recognizing the WNV NS4B within infected cells, also recognized the NS4B Protein expressed at the time of transfection. From these results it is clear that the JEV NS4B Antibody is specific to NS4B of WNV but not to NS4B Protein of the4 DENV serotypes. The specificity of this Antibody might be secondary to the visible alterations that are present among the amino acid sequence identity as well as antigenic association within the NS4B Protein of WNV, DENV as well as JEV [48].

Japanese encephalitis (JE) is a mosquito borne viral infection of brain which might result in permanent brain damage as well as death. In Philippine's, work is being done to develop a live attenuated JE vaccine (CD-JEV) to children <5yr of age (YOA), who get disproportionately infected. Lot of Vaccination approaches are under consideration. Thus Vodicka E., *et al*. carried out a cost effective evaluation that compared 3 Vaccination approaches to the present status of no Vaccination from the societal and government perspectives: 1) national routine Vaccination only, 2) sub-national campaign followed by national routine, and 3) national campaign followed by national routine. They formed a Markov model for evaluating the effect of Vaccination or no Vaccination over the child's lifetime horizon, presuming an annual incidence 10.6 cases/100,000. Cost of illness ($859/case), vaccine (%0.50/dose), routine Vaccination ($0.95/dose), as well as campaign Vaccination ($0. 98/dose) were on the basis of hospital financial records, expert opinion awa literature. The societal perspective included transportation as well as opportunity costs of caregiver time, besides the costs borne by the health system. JE Vaccination through national campaign followed by national routine delivery was the most cost effective approach modelled with a cost/disability adjusted life year (DALY) averted of $233 and $29 from the government as well as societal perspective, respectively. JE Vaccination was aimed to avoid 27,856 -37,277 cases, 5571 - 7455 deaths, and 173,233 - 230,704 DALY's among children <5 over 20 consecutive birth cohorts. Complete incremental costs of Vaccination versus no Vaccination over 20 birth cohorts were $6.6 - $9.8 million from the societal perspective ($230K - $440K annually) as well as $45.9 - $53.9 million ($2.2M - $2.7M annually) from the government perspective. Thus concluding that Vaccination with CD- JEV In the Philippines is found to be cost-effective, decreasing long term cost s correlated with JE illness as well as improving health results as compared to no Vaccination [49].

Live attenuated vaccine (SA-14-14-2 strain) is the commonest used JE Vaccination, with clinical data having corroborated its safety as well as efficacy. Eight areas related to the virulence of the Envelope (E) protein, are usually the centre of quality control of JE Vaccine. But sequences got out of NCBI. along with earlier results Yang., *et al.* demonstrated that the wild strain SA 14 might harbour 2 separate amino acids at amino acid residue 244 of the E glycoprotein (E244) and it might be correlated with the virulence. Here they introduced a single mutation at n1708 (G-→A) in the full length cDNA clone of SA-14-14-2, replacing a Gly with Glu at amino acid residue 244 of the E glycoprotein, and morphology as well as growth characteristics of JEV SA-14-14-2 in cell culture. But it had lethal neurovirulence in mice and could enter the brain after intraperitoneal inoculation. Further, the virulence of JEV E244 in the relation of vaccine in mice is significantly separate from that of the genetic stability of the attenuated JE vaccine. Finding of minor mutations in vaccine population along with effect of the safety of vaccine was detailed [50].

Conclusion

Thus in this review we have shown Japanese encephalitis is caused by a flavivirus called Japanese encephalitis virus. Both JEV and WNV share certain ecological similarities since they maintain

an enzootic transmission cycle with various bird families as natural reservoirs and mosquitoes of the Culex species as main vectors. Despite international presence till date no specific therapies exist with acute cases leading to severe presentation and survivors may be left with neurological sequelae. Till now all patients of encephalitis are started with acyclovir as the 2 cases reported to start with and intravenous immunoglobulins, blood transfusion and active ICU care is given MRI shows specific presentation in basal ganglia, thalami, and EEG is needed to see if anticonvulsants are needed. Role of steroids remains controversial. With the looking for newer therapies orlistat a pancreatic lipase inhibitor is being tried for various viral infection as well as certain cancers in view of unavailability of fuel for the replicating cells. Other innovative drugs are being tried. Vaccinations are cost effective but not used routinely. Need of the hour is to get specific therapies against JEV. JE stimulates mast cell specific chymase at the time of its penetration via blood brain barrier (BBB) and its inhibitors are being tried as innovative agents. Similarly phytoconstituents of genus Arisaemia against different targets (NS5, NS3 helicase NS2B-NS3 protease) of JEVs that exhibit key role in replication, infection cycle as well as host interactions by using molecular docking and then molecular dynamics (MD) simulations are being looked into by virtual screening docking methods.

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