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Review Article

Japanese Encephalitis: Bangladesh Perspective: A Review

Sultana M Hussain[1], A R M Saifuddin Ekram [2], M J Hossain [3], E Gurley [4], S Lubey[5]

Abstract

Japanese encephalitis is numerically one of the most important causes of mosquito borne viral encephalitis not only in Asia but all over the world. Japanese encephalitis infection has not been recognized in Bangladesh since an outbreak in 1977 near Mymensingh. A prospective hospital based surveillance study carried out by Centre for Health and Population Research (ICDDR,B) and the Centers for Disease Control and Prevention (CDC), USA began in June 2003 at Dhaka, Mymenhsingh and Rajshahi Medical College Hospital to find out the causes of encephalitis proved that there are 6% patient who were admitted to the hospital with the sign and symptoms of encephalitis were infected with JE. In Rajshahi Medical College Hospital 12.38% encephalitic patients had JE infection. Though the study is ongoing but these data suggest that Japanese encephalitis virus is an emerging cause of encephalitis in Bangladesh.

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Introduction

Japanese encephalitis is a common mosquito-borne viral encephalitis found in Asia. Most infections of JE are asymptomatic but if clinical illness develops, it causes significant morbidity and mortality. It is numerically one of the most important causes of viral encephalitis not only in Asia but also all over the world. Though under reported, Japanese encephalitis causes an estimated 50,000 cases and 15,000 deaths annually.[1] About one third of patients die, and half of the survivors have severe neuropsychiatric sequelae suffering from the disease.[2] The disease was confound mostly to rural areas of Asia but now it is spreading at an alarming rate. Multiple factors such as occupation, recreational exposure, gender (possibly reflecting exposure), previous vaccination, and naturally acquired immunity alter the potential for infection and illness. A higher case-fatality rate is reported in the elderly, but serious sequelae are more frequent in the very young, possibly because they are more likely to survive a severe infection.

History

The outbreak of encephalitis attributed to JE virus (JEV) were reported in Japan as early as 1871.[3] But major epidemics were reported about every 10 years, with more than 6000 cases reported in the 1924 epidemic[4] and Japanese encephalitis virus was first isolated from a fatal case in the 1930s.[2] The Nakayama strain of JEV, used in development of mouse brain to produce inactivated virus vaccine was first isolated in 1935.[5] The mode of transmission by mosquito vector was elucidated

[1] Project Research Physician, ICDDR, B, Mohakhali, and Dhaka.
[2] Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.
[3] Assistant Scientist, ICDDR, B, Mohakhali, Dhaka.
[4] Program Co-ordinator, ICDDR, B, Mohakhali, and Dhaka.
[5] Head, Programme on Infectious Diseases and Vaccine Sciences, ICDDR, B, Mohakhali, Dhaka.

only 25 years after recognition of JEV[5]. Until 1970, the temperate zone of Asia was the principal site of JE transmission. In the last three decades, the focus of viral epidemics has switched over to South and Southeast Asia. The virus was later classed as a member of the genus Flavivirus (family *Flaviviridae*) named after the prototype yellow fever virus (Latin; yellow=flavi). Although of no taxonomic significance, the ecological term arbovirus is often used to describe the fact that Japanese encephalitis virus is arthropod borne.[2]

Epidemiology

Neurotrophic Flavivirus: A global perspective

Japanese encephalitis virus is transmitted between animals by Culex mosquitoes, and occurs across eastern and southern Asia and the Pacific rim. However, related neurotrophic flaviviruses are found across the globe sharing many virological, epidemiological, and clinical features.[6] Molecular virological studies suggest that all flaviviruses derived from a common ancestor some 10-20 000 years ago, and are rapidly evolved to fill ecological niches.[7] Examples of mosquito borne neurotrophic flaviviruses include Murray Valley encephalitis virus in Australia, and St Louis encephalitis virus in North America. West Nile virus, also a flavivirus found in Africa, the Middle East, and parts of Europe, is traditionally associated with a syndrome of fever, arthralgia and rash, and with occasional nervous system disease. But in 1996 West Nile virus caused an outbreak of encephalitis in Romania[8] and a West Nile-like flavivirus was responsible for an encephalitis outbreak in New York in 1999.[9] In northern Europe and northern Asia, flaviviruses have evolved to use ticks as vectors. Far eastern tick-borne encephalitis virus (also known as Russian spring-summer encephalitis virus) is endemic in the eastern part of the former USSR, and Western tick-borne encephalitis virus occurs in Europe and has caused recent epidemics in Germany and Austria.[10]

Enzootic Cycle

Japanese encephalitis virus is transmitted in a zoonotic cycle among mosquitoes and vertebrate-amplifying hosts, chiefly pigs and wading birds. The mosquito vector of JE differs in different regions. JEV has been isolated from 10 different species of Culex, four species of Anopheles, and three species of Mansonia mosquitoes.[11] But the most important human infection spreads by *Culex tritaeniorrhynchus* and *Culex vishnui* groups which breeds in pools of stagnant water (such as rice paddy fields). [12, 13] Although many animals can be infected with the virus, only those which develop high viraemias are important in the natural cycle. As well as maintaining and amplifying Japanese encephalitis virus in the environment, birds may also be responsible for the spread to new geographical areas. Pigs are the most important natural host for transmission to humans, because they are often kept close to humans, have prolonged and high viraemias, and produce many offspring. The virus does not typically cause encephalitis in these natural hosts, although abortions occur in pregnant sows.[2]

Epidemiology of Human Disease

Humans become infected with Japanese encephalitis virus coincidentally when living or travelling in close proximity to the enzootic cycle of the virus. Although most cases occur in rural areas, Japanese encephalitis virus is also found on the edge of cities. Epidemiological studies have shown that after the monsoon rains mosquitoes breed prolifically, and as their numbers grow, spread of JEV virus and the infection rate of pigs and wading birds grow simultaenously.[14,15] Human infection soon follows. In sentinel studies, previously unexposed pigs placed in endemic areas were infected with the virus within weeks.[2]

Although the virus has occasionally been isolated from human peripheral blood[16] viraemias are usually brief and titers low; thus humans are considered a dead end host from which transmission does not normally occur. However, the risk of acquiring JE in laboratory settings does exist. Cross sectional serological surveys have shown that in rural Asia most of the people are infected with Japanese encephalitis virus during childhood or early adulthood.[17] About 10% of the susceptible people are infected every year.[18]

However, most infections of humans are asymptomatic or result in a non-specific flu-like illness.

Japanese encephalitis is mostly a disease of children and young adults. In northern Thailand the estimated rate to be is 40 per 100,000 for 5 to 25 year age group and infected it declines to almost zero for those over 35 years.[17] The incidence is lower among young children (<3 years old) than in older children, possibly reflecting behavioural factors- for example, playing outside after dusk.[19]

When epidemics first occur in new locations, such as in Sri Lanka, India, and Nepal, adults are also affected.[20] Broadly speaking two epidemiological patterns of Japanese encephalitis are recognised.[19] In northern Asia (northern Vietnam, northern Thailand, Korea, Japan, Taiwan, China, Nepal, and northern India) huge epidemics occur during the summer months, whereas in southern Asia (southern Vietnam, Southern Thailand, Indonesia, Malaysia, Philippines, Sri Lanka, and southern India) Japanese encephalitis tends to be endemic, and cases occur sporadically throughout the year with a peak after the start of the monsoon.[19]

Various explanations for this different pattern have been suggested. JEV isolated from epidemic northern Thailand and endemic southern Thailand were of different genotypes which suggests different neurovirulence among different strains may be responsible for various presentation.[21] However, data from Vietnam do not support this, rather comparisons of climate of northern and southern Vietnam suggest that temperature may be an important factor.[22] Rainfall patterns are almost identical in northern and southern Vietnam but the temperature is very different, and the number of cases of encephalitis seems to follow temperature closely.

Geographical Distribution

In the past 50 years the geographical area affected by Japanese encephalitis virus has expanded. Differences in diagnostic capabilities and in reporting of encephalitis make it impossible to plot this expansion precisely. However, the timing of the first reported cases or new epidemics in each area gives an impression of the relentless spread of Japanese encephalitis. In China outbreaks of summer encephalitis occurred from 1935, and the virus was first isolated there in 1940.[19] In the far eastern Russian states, Japanese encephalitis first occurred in 1938. In 1949, large epidemics were reported from South Korea for the first time. Epidemics in northern Vietnam followed in 1965, and in Chiang Mai in northern Thailand in 1969. Japanese encephalitis was found in southern India from 1955, but was confined to the south until the 1970s. Since then, large outbreaks have been reported from eastern and northeastern states. The late 1970s JE cases were first seen in Burma and Bangladesh, and large epidemics in southwestern Nepal. Since then Japanese encephalitis infection has not been recognized in Bangladesh.[23] In 1985 Sri Lanka experienced its first epidemic with 410 cases and 75 deaths. JEV continue to spread west with cases occurring in Pakistan[24] and new epidemics in the Katmandu valley of Nepal.[25] The disease has occurred on the western Pacific islands with outbreaks in Guam in 1947[26] and Saipan in 1990.[27] Japanese encephalitis is endemic in Malaysia and Indonesia. It occurs sporadically in the Philippines and New Guinea. The first case occurred in the Australian Torres Straits islands in 1995,[3] and it was reported for the first time north of Cairns on the Australian mainland in 1998.[28]

Virology

Japanese encephalitis virus (JEV) is a member of the Flaviviridae. It has a spherical virion, a small (50 mm) lipoprotein envelope surrounding a nucleocapsid comprising of core protein and 11 kb single stranded RNA (3800 KD) [29]. The M protein containing hydrophobic domains presumably serves as a transmission anchor.[30] E protein constitutes the major immunogen and is also expressed on the plasma membrane fusion and cell entry.[32] These suggest that the E protein has a major role in determination of virulence phenotype, and that single amino acid substitutions are sufficient to cause neurovirulence or neuroinvasiveness.[33] The protein is the major target of the host antiviral immune response.[34]

Pathology

Grossly, the brain appears oedematous with changes mainly involving gray matter. The most commonly affected areas are the thalamus, substantia nigra, anterior horns of the spinal cord, cerebral cortex, and cerebellum. Microscopy reveals pan encephalitis with abundant glial nodules, perivascular cuffing, and necrosis with or without characteristic circumscribed necrotic foci.[35-37] Neuronal inflammation is typically associated with mononuclear cell infiltration. microglia proliferation and formation of glio-mesenchymal nodules in brain parenchyma dominate the histological picture in acute encephalitis. In the post-encephalitic phase, lesions become linear and tend to localize in thalamus, substantia nigra, and Ammon's horn. Histopathological examination of these focal lesions show rarefied areas with few cellular and fibrous elements surrounded by dense glio-mesenchymal scarring.[38, 39]

Pathological changes described in extra neural tissues include hyperplasia of germinal centers of lymph nodes, enlargement of Malpighian bodies in spleen, interstitial myocarditis, swelling and hyaline changes in hepatic Kuffer's cells, pulmonary interalveolitis, and focal haemorrhages in the kidney.

Pathogenesis

After transmission to man by an infected vector mosquito, Japanese encephalitis virus multiplies locally and in regional lymph nodes.[40] After a phase of transient viraemia, invasion of the central nervous system (CNS) occurs. JEV is thought to invade brain via vascular endothelial cells by endocytosis.[41] In the neurons, JEV replicates and matures in the neuronal secretory system, mainly the rough endoplasmic reticulum and Golgi apparatus, eventually destroying them.[42] Experimental studies in mammalian hosts have shown JEV tropism to neurons in the CNS, indirectly indicating the presence of specific receptors with strong affinity for the virus.[43]

Immunology

Both humoral and cellular arms of immune system are involved in immunity to Japanese encephalitis virus. But the relative contribution of individual components has not been well understood. After primary infection with JEV, a rapid and potent monotypic IgM response occurs in serum and cerebrospinal fluid (CSF), usually within seven days.[44] the role of antibodies in protection is not yet clearly understood. Disappearance of neurological signs has been noted in the presence of IgM antibodies.[45] Presence of CSF IgM antibodies has been correlated with a favorable outcome in JE.[46] However, the significance of this protection remains unknown, since neurovirulence of JEV has been enhanced by administration of virus specific antibodies.[47] An anamnestic antibody response with an early rapid IgG and delayed slow IgM response has been noted in patients previously infected with antigenically related flaviviruses.

Clinical feature

Children under 15 years of age are principally affected in endemic areas. When JEV first affects a nascent population, adults are also affected. Infection with JEV is often asymptomatic. Man to man transmission has not been reported. The incubation period of JEV in man, after a mosquito bite, is not exactly known. In general, it varies from 1-6 days. However, it can be as long as 14 days.

Onset of the illness can be abrupt, acute, sub acute, or gradual. The course of the disease can be conveniently divided into three stages: (i) a prodromal stage preceding CNS features, (ii) an encephalitis stage marked by CNS symptomatology, and (iii) a late stage noticeable by recovery or persistence of signs of CNS injury.[48]

The prodromal stage is characterized by few days of non-specific febrile illness, which may include coryza, diarrhoea, and rigors. This is followed by headache, vomiting, and a reduced level of consciousness, often heralded by a convulsion. During this stage, a definitive clinical diagnosis is

not possible. This is followed by the encephalitis stage (third to fifth day), which manifests with altered sensorium, convulsions, neck stiffness, muscular rigidity, mask-like facies, and abnormal movements.[5]

The classic description of Japanese encephalitis includes a dull flat mask-like facies with wide unblinking eyes, tremor, generalized hypertonia, and cogwheel rigidity. These features were reported in 20%-40% of Indian children.[6] Abnormal oculocephalic reflex, acute onset hemi paresis with hypertonia and decorticate and decerebrate posturing are important CNS signs, which help in early clinical identification of intracranial hypertension.[5] Opisthotonus and rigidity spasms, particularly on stimulation, occur in about 15% of patients and are associated with a poor prognosis. Other extra pyramidal features include head nodding and pill rolling movements, opsoclonus, myoclonus, choreoathetosis, and bizarre facial grimacing, and lip smacking. Upper motor neuron facial nerve palsies occur in around 10% of children and may be subtle, or intermittent.[6] Features of extra neural involvement reported in JE includes gastric haemorrhage in absence of bleeding diathesis and pulmonary oedema. Death usually occurs due to neurological illness in the first week.

Children who survive slowly regain neurological function over several weeks. Residual neurological impairment includes thick, slow speech, aphasia, and paresis. Only one third of cases recover normal neurological function. Intellectual involvement may be noted in 30% of cases, speech disturbance in 34%, and motor deficits in 49%. Secondary infections, especially pneumonia, urinary tract infection, and stasis ulcers are frequent complications during recovery period.[5]

Apart from the classical presentation, a proportion of patients recover spontaneously (so called abortive encephalitis). Others may present with aseptic meningitis and have no encephalopathic features.[49] In some children a single convulsion is followed by a rapid recovery of consciousness, resulting in a clinical diagnosis of febrile convulsion. Again some patients, particularly older children and adults, abnormal behaviour may be the only presenting feature, resulting in an initial diagnosis of mental illness. Generalized tonic-clonic seizures occur more often than focal motor seizures. Multiple or prolonged seizures and status epilepticus are associated with a poor outcome (Solomon T *et al*, unpublished observations).[6] In a proportion of children subtle motor seizures occur, causing twitching of a digit, eye, or mouth, eye deviation, nystagmus, excess salivation, or irregular respiration. Without electroencephalographic monitoring these may be difficult to identify (Solomon T *et al*, unpublished observations).[6]

Changes of respiratory pattern, flexor and extensor posturing, and abnormalities of the pupillary and oculocephalic reflexes are poor prognostic signs[49] and may reflect encephalitis in the brain stem.[6] Recently a subgroup of patients have been identified infected with JEV presented with a poliomyelitis-like acute flaccid paralysis.[50] After a short febrile illness there was a rapid onset of flaccid paralysis in one or more limbs, despite a normal level of consciousness. Weakness occurred more often in the legs than in the arms, and was usually symmetric. Thirty per cent of such patients subsequently developed encephalitis, with reduced level of consciousness, and upper motor neuron signs, but in most acute flaccid paralysis was the only feature.[50]

Investigations

A peripheral neutrophillic leukocytosis is seen in most patients, and hyponatraemia may occur as a consequence of inappropriate antidiuretic hormone secretion (SIADH). The CSF opening pressure is increased in about 50% of patients. High pressures (>250 mm) are associated with a poor outcome (Solomon T *et al*, unpublished observations). Typically there is a moderate CSF pleocytosis of 10-100 cells/mm^3, with predominant lymphocytes, mildly increased protein (50-200 mg%), and a normal glucose ratio. However, polymorph nuclear cells may predominate early in the disease, or there may be no CSF pleocytosis.[6] Features on an electroencephalogram (EEG) show great diversity

and are non-specific showing diffuse theta and delta waves, burst suppression, epileptiform activity, and alpha coma. The generalized changes in an EEG may help in differentiating JE from herpes encephalitis.[5]

CT scan of half of the patients show bilateral non-enhancing low density areas in the thalamus, basal ganglia, midbrain, pons, and medulla.[6] Cortical atrophy has been noted in some children in the post-encephalitic phase. Magnetic resonance imaging is more sensitive and demonstrates more extensive lesions of the thalamus, cerebrum, and cerebellum on T2-weighte.[51] Imaging studies may be useful in distinguishing Japanese encephalitis from herpes simplex encephalitis, because in JE the lesions are mainly seen in the diencephalons and basal ganglia whereas in herpes encephalitis the changes are characteristically fronto-temporal.[6] Single photo emission tomography (SPECT) carried out in acute cases may show hyper perfusion in the thalamus and putamen. Though these neuroimaging techniques demonstrate significant changes but they are too non-specific to use for aetiological diagnosis.

Etiological diagnosis

Etiological diagnosis of JE is based on virus isolation or identification of virus specific antigen or antibodies in CSF or blood. The laboratory diagnosis of Japanese encephalitis is confirmed by one of the following:

1. Fourfold or greater rise of antibody titre in serum, or
2. Isolation of virus from or identifying viral antigen or genomic sequences in tissue, blood, CSF, or other body fluid, *or*
3. Specific IgM antibody by enzyme immunoassay antibody captured in CSF or serum.

Culture

JEV was conventionally isolated by intracerebral inoculation of clinical specimens in suckling mouse brain. Various cell cultures; primary chick, duck embryo cells, and lines of Vero, LLCMK$_2$, C6/36, and AP61 cells are recently in use.[5] Virus can be isolated from the blood of patients in pre-neuroinvasive and neuroinvasive phases of the illness, usually within six or seven days after the onset of symptoms.[52] However, isolation of virus from clinical specimens is a rare occurrence[16] probably because of low viral titres, rapid production of neutralizing antibodies, and the logistic difficulty in transportation of specimens in developing countries and frequent freezing and thawing of clinical material.[53] Mosquito inoculation techniques have been adopted for isolation of JEV now a days.[5] Complement fixation test and agar gel diffusion was traditionally carried out to identify JEV in culture substrates. Now neutralization test, monoclonal-based immunofluorescence technique, and enzyme immunoassay are in use.[5]

Antigen detection

Detection of antigen in CSF by reverse passive haemagglutination, immunofluorescence, and staphylococcal co agglutination tests using polyclonal or monoclonal antibodies are efficacious in rapid diagnosis of JE.[5] MIGSS like modified techniques have been successfully tried in the detection of antigen in mononuclear cells of peripheral blood and CSF of patients.[54]

Antibody detection of virus

Now a day to identify virus specific antibody in both blood and CSF IgM antibody capture ELISA (Mac-ELISA) is the method of choice. When serum IgM antibodies are used for confirming JE, the co-presence of IgG antibodies should be measured by another serological assay. Avidin biotin system (ABC Mac-ELISA), biotin labeled immunosorbent assay to sandwich ELISA, nitrocellulose membrane based IgM capture dot enzyme immunoassay (Mac DOT), and antibody capture radio immunoassay (ACRIA) are some of the newer modifications of Mac-ELISA.[5] Other serological tests such as haemagglutination inhibition, the complement fixation test, single radial haemolysis, and the neutralization test are still in use.

Differential Diagnosis

The differential diagnosis of Japanese encephalitis is broad. They include both infective and non-infective conditions affecting the CNS. Infectious diseases include other viral encephalitis (Arbovirus, Herpes virus, Nipah virus, Enterovirus, and post infectious and post vaccination encephalomyelitis), other infectious diseases with CNS manifestations (typhoid encephalopathy, febrile convulsions). Non-infectious diseases are tumours, cerebrovascular accidents, Reye's syndrome, toxic and alcoholic encephalopathies, and epilepsy.[5] Where other flaviviruses are endemic they should also be included in the differential diagnosis. Even viruses that are not usually neurotrophic may cause encephalitis, such as West Nile virus and dengue viruses and only with appropriate diagnostic tests these viruses can be distinguished from Japanese encephalitis virus.[55]

Management

There is no specific treatment for Japanese encephalitis rather the treatment is supportive and symptomatic. It involves controlling convulsions and raised intracranial pressure when they occur. Corticosteroids are used in routine practice, but a double blind randomized placebo controlled trial of dexamethasone demonstrated no benefit.[56] To reduce the risk of complications like; bed sores, malnutrition, contractors, aspiration pneumonia careful nursing care and physiotherapy are needed. In vitro utility isoquinolone compounds are effective.[57] Interferon-α is currently the most promising potential treatment.[6] In response to infection with Japanese encephalitis virus it (interferon-α) is produced naturally in the CSF.[37] Recombinant interferon-α has been given in open trials to a few patients with encouraging results, and is a placebo controlled double blind trial is on going.[58]

Though there is no specific drug against JE, mortality and morbidity can be reduced by treating the factors causing secondary deterioration. The value of this approach has been documented in traumatic coma, [59] and has been effectively applied in Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India in management of JE.[5] Reduction of intracranial pressure, optimization of systemic arterial pressure to maintain adequate cerebral perfusion, and prevention of secondary complications are the main objectives of treatment.

If intracranial hypertension is present, and cerebral perfusion pressure is less than 40 mm Hg, auto regulation of cerebral blood flow is impaired.[60] When auto regulation is impaired, the degree of cerebral ischaemia is significantly worsen due to lack of functional integrity of cerebral blood vessels, especially in conditions like viral encephalitis. Even minor degrees of hypotension or intracranial hypertension may markedly aggravate cerebral ischaemia.

To maintain intracranial hypertension, early detection and instant treatment with appropriate drugs is necessary. Once irreversible cerebral damage is established treatment with therapeutics is of no use. The control of intracranial hypertension involves two approaches: control the situations that exacerbate intracranial pressure and therapeutic measures to decrease intracranial hypertension, if present.

Control the situations aggravating intracranial pressure

Posturing the patient

The head should be in the midline in 15-30^0 tilting up position that decreases intracranial hypertension and improves cerebral perfusion pressure.[61] Elevation enhances CSF drainage and maximizes cerebral venous output.

Control temperature

Fever worsens intracranial hypertension by increasing cerebral metabolism, cerebral blood flow, and cerebral oedema[62]. So fever should be treated aggressively. Antipyretics and other physical measures like tepid sponging should be employed. Shivering can aggravate intracranial hypertension so appropriate measures should be taken to reduce it.

Sedation

Increased cerebral blood flow can raise intracranial pressure. Sedatives can prevent the worsening of intracranial hypertension.[56] Conventionally sedatives were avoided, in fear of "clouding the neurological examination".

Seizure Control

Seizures increase intracranial pressure by increasing cerebral metabolism and cerebral blood flow and by Valsalva. So anticonvulsants should be administered prophylactic ally or therapeutically.[5]

Fluid and electrolyte management

Conventional thinking was fluid and sodium should be restricted to the patients to prevent cerebral oedema. However dehydration increases the risk of cerebral infarction in patients with subarachnoid haemorrhage.[63]

Hypovolaemia often accompanies viral encephalitis due to decreased intake and increased loss (vomiting, sweating). Fluid should be restricted to those who are in various grade of coma and central venous pressure can be measured to guide fluid therapy. Full maintenance of sodium should be given as hyponatraemia impairs cerebrovascular reactivity and serum sodium level should be maintained above 140mmol/l.

Therapeutic Measures to Decrease Intracranial Hypertension

Hyperventilation

Hyperventilation causes reduction in intracranial pressure by decreasing cerebral blood flow secondary to cerebral vasoconstriction caused by carbon dioxide washout. Though hyperventilation is useful to decrease intracranial pressure rapidly but prolonged hyperventilation worsens the outcome. This could be probably due to production of oligaemia in marginally perfused brain tissue.[64] To avoid this grave condition, hyperventilation should gradually be withdrawn (rapid withdrawal causes rebound intracranial hypertension) after a 30-60 minutes.[65]

Mannitol

Mannitol is the most commonly used agent to control intracranial hypertension. Response to mannitol depends on intracranial pressure, dose given over the previous three hours[66] and rate of administration. Rapid administration of mannitol is more effective in reducing intracranial pressure, but the action has a much shorter duration.[5] A slower infusion rate produces a lesser degree of decrease but the effect lasts longer.[67] Though mannitol is a very useful drug, it can cause significant side effects if used inappropriately. Mannitol accumulate in oedematous white matter and produce a hyper osmolar state, which is injurious to the brain.[68] Use of mannitol should be limited to patients with a serum osmolality of less than 300 mmol/l.[69] Because administration of mannitol at a dose of 1g/kg over a period of 20 minutes increases serum osmolality by 11%-15%, [70] and tends to a high risk of tubular damage and renal failure when serum osmolality exceeds 330 mmol/l.

Frusemide

It interferes with the formation of CSF.[71] Frusemide alone causes a slow reduction in intracranial pressure, but when combined with mannitol, the fall in intracranial pressure is rapid and is sustained for a considerably longer period.[72]

Barbiturates

Continuous infusion of short acting barbiturates like thiopentone, evoke a decrease in intracranial pressure by decreasing cerebral blood flow and cerebral metabolic oxygen demand.[73] Barbiturate therapy has the added advantage of causing sedation, which by itself can contribute to reduction of intracranial hypertension. Unfortunately, barbiturate therapy posses major adverse effect, including precipitating hypotension[74], and hence should be used only when other measures have failed.[5]

Monitoring

While treating the patient careful attention should be given to monitor the coma scale score, seizure

type and frequency, clinical signs of intracranial hypertension, blood pressure in every hour, urine output in every four hour (it should be maintained at 0.5ml/kg/hour), serum osmolality in every 24 hours, temperature and central venous pressure for severe coma.

Outcome

About 30% of patients admitted to hospital with Japanese encephalitis die, and around half of the survivors have severe neurological sequelae.[2] However, where is better hospital facilities are available a reduction in mortality, but concomitant increase of disease sequelae is seen.[2] About 30% of survivors have frank motor deficits including a mixture of upper and lower motor neuron weakness, and cerebellar and extra pyramidal signs, fixed flexion deformities of the arms, and hyperextension of the legs with "equine feet" are common.[75] Twenty percent of patients have severe cognitive and language impairment (most with motor impairment also), and 20% have further convulsions.[51,76] A higher rate of sequelae is reported for children than adults.[77] More detailed

studies have shown that about half of those who have good recovery have more subtle sequelae such as learning difficulties, behavioural problems and subtle neurological signs.[51]

Prevention

Japanese encephalitis prevention includes those practices, which interfere with the enzootic cycle of the virus, and those, which prevent disease in humans.

Vector control

For JE control the information of prevalence, density, and insecticide susceptibility of potential vectors of JE is essential. Surveillance of the adult mosquito population should be carried out throughout the year. To control Culex mosquitoes' breeding larvicides to rice fields, and insecticide should be sprayed. Thermal fogging with ultra low volume insecticides such as pyrethrum or malathion has been recommended for the prevention of local transmission during epidemics, particularly in periurban areas with marshes. The vastness of breeding places make larvicidal measures ineffective now a days.[13] Water management and irrigation practices such as periodic lowering of the water level, intermittent irrigation, and constant flow systems are effective measures adopted by some countries to limit larval development.

Prevention of mosquito bite

To avoid and minimize mosquito-biting use of nets and mosquito repellents, avoidance outdoor sleeping in the tropics in dusk and dawn, staying screened houses, and wearing long sleeved clothing[6] should be adopted.

Protection of reservoir

Piggeries should be built away from dwellings. In countries where pigs are reared near human settlement piggeries being mosquito proof is desirable. Spraying of piggeries and mixed dwelling with residual insecticides. Wherever there is an alarming rise in vector species, should be carried out promptly. Vaccination of pigs has shown encouraging results.

Vaccination

Formalin inactivated vaccines against Japanese encephalitis were produced in Russia, Japan, and in the United States by Albert Sabin (later of polio fame).[78] Similar formalin inactivated vaccine has been manufactured in Japan produced by Osaka University and is available internationally under the BIKEN label. Similar vaccines are made by others manufacturers in India, Japan, Korea, Taiwan, Thailand, and Vietnam. Three doses of vaccine are required to give protective antibody levels it is given at 0, 7, and 30 days, with a booster immunization recommended at 1 year.[5]
Chinese authorities licensed a new live attenuated Japanese encephalitis vaccine in 1988. The vaccine (SA 14-14-2) was produced by passing the virus through weanling mice, then culturing in primary baby hamster kidney cells. It has been given shot over 100 million in China and proved to be immunogenic and safe. The effectiveness of

one dose was 80% and of two doses 1 year apart 97.5%. [79] Another inactivated JE vaccine based on the same SA 14-14-2 strain is currently being developed by a US company (VaccGen) and tested in Phase II in Thailand, China as well as Japan is now producing vero cell derived inactive JE vaccines and Biken and Chemo-Sero Therapeutic Research Institute are testing these vaccines in Phase I-II trial. Chimeric vaccine concept of live-attenuated vaccines using the 17D yellow fever strain cultivated on Vero cells has been developed by Acambis recently. The prototype vaccine has been tested successfully in US adults, showing good safety and immunogenicity. A trial in a JE-endemic country in adults and children is planned in 2003.[80]

Side effect

There are several side effects of JE vaccination. Among them local side effects include tenderness, redness, swelling. Sometimes systemic adverse reactions are also noticed like fever, headache, malaise and rash. Occasionally generalized urticaria, angio-oedema, respiratory distress, and anaphylaxis like hypersensitivity reaction may be noticed. And very rarely major neurological side effects (1-2.3 per million recipients: encephalitis, seizures, and peripheral neuropathy) could be observed.[6] Second generation recombinant vaccines are being developed with the aim of improving immunogenicity and decreasing adverse reactions.[5]

Who should be vaccinated?

The population who should be vaccinated depends on epidemiological factors. All people living in endemic area except infants need to be vaccinated. However for infants precautions to avoid mosquito bite should be taken. The use of JE vaccine in travelers should be decided after adequate consideration like the risks for exposure to the virus and, the availability and acceptability of repellents and other alternative protective measures, and the side effects of vaccination. However, travelers who are likely to spending more than 30 days in an endemic area or less than 30 days during epidemics or extensive outdoor activity in rural areas are expected to be vaccinated. Laboratory workers with potential risk of exposure to JEV should also take vaccines.

Bangladesh perspective

Culex mosquitoes are unavoidable in agro-based rural Bangladesh, and almost everyone is exposed to the virus. Intensification and expansion of irrigated rice production systems and Bangladesh over the past few years have had in important impact on the disease burden caused by JEV. The flooding of the fields at the start of each cropping cycle leads to an explosive build-up of the mosquito population. This may cause the circulation of the virus to spill over from their usual hosts (Birds and pigs) into the human population. The epidemic situation of Japanese encephalitis in Bangladesh needs to be clarified.[80] Japanese encephalitis infection has not been recognized in Bangladesh since an outbreak in 1977 near Mymenshing.23 A prospective hospital-based surveillance study carried out by Center for Health and population Research (ICDDR, B) and the Centers for Disease Control and Prevention (CDC) Atlanta and Ft. Collins, USA began in June 2003 at Dhaka, Mymensingh and Rajshahi Medical College Hospital to find out the causes of encephalitis proved that there are 6% patient who were admitted to the hospital with the sign and symptom of encephalitis were infected with JE.[81] In Rajshahi Medical College Hospital 13 out of 105 (12.38%) patients had Japanese encephalitis infection demonstrated by a four-fold rise in virus-specific antibody detected in paired acute and convalescent sera by enzyme-liked immunosorbent assay and validated by ruling out dengue through enzyme-liked immunosorbent assay testing and subsequent plaque reduction neutralizing testing for virus specificity of the antibody,[82] Through the study is ongoing but these data suggest that Japanese encephalitis virus is an emerging cause of encephalitis in Bangladesh. The epidemiology has recently been complicated by a superimposed epidemic of an encephalitic virus previously unidentified in Bangladesh. This RNA paramyxovirus (Nipah virus), which is similar to the Australian Hendra virus, was first detected in

Malaysia and seems to be transmitted to humans from other vertebrates (fruit bat and pigs). In Bangladesh, the diagnostic facilities for Japanese encephalitis and other viruses causing encephalitis are limited. Rapid diagnosis and early treatment of viral encephalitis are vital to reduce mortality and disability. Specific treatment for Japanese encephalitis is not available. Control is the only procedure to reduce mortality and morbidity caused by the disease which is based on rapid recognition of early cases, subsequent immunization of persons or animals at risk, or immunization of persons or animals with the potential to be at risk, such as travelers, laboratory personnel, and attending clinicians as well as mosquito control (spraying, impregnated bed nets), pig control (segregation, slaughtering etc.) should be given priority.

Further approaches

Despite formalin inactivated vaccination achieved some success, and new live attenuated vaccines are promising, Japanese encephalitis remains as an important public health problem into the next millennium. As for smallpox and polio, humans are the only host so eradication of those diseases by vaccination is feasible; the enzootic nature of Japanese encephalitis virus makes it impossible of global eradication. The geographical area affected by JE is expanding, as a result 2.8 billion people living in affected areas will continue to be exposed to the virus.[6] Thankfully, only a small proportion of them develops disease. The recent discovery of a poliomyelitis-like presentation of Japanese encephalitis virus in Vietnam raises important questions, especially as the target for global eradication of polio approaches. Is this Japanese encephalitis virus myelitis unique to Vietnam, or it also persists in other JE endemic areas? Has it recently arisen, or it affected patients who were previously labeled as having polio? The viral and host factors that determine who develops disease and which are responsible to determine different clinical presentations need further investigation.

Considering the many cases of Japanese encephalitis, research into antiviral drugs has been relatively neglected. Interferon-α, which was shown to be effective in vitro is now being assessed in human disease. Newer antiviral drug, and their possible role should be assessed in treating Japanese encephalitis. JEV is expanding across the globe at an alarming rate. New rapid diagnostic methods should be adopted to monitor the spread of the disease in locations where, the etiology of encephalitis is still guessed. The environmental and ecological factors responsible for the spread of JE need further investigations, with a view to control the spread of this fascinating and devastating disease.

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All correspondence to:
A R M Saifuddin Ekram
Professor, Department of Medicine
Rajshahi Medical College, Rajshahi-6000.