

Japanese Encephalitis— A Perspective

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Japanese encephalitis is numerically one of the most important causes of viral encephalitis worldwide, with an estimated 50,000 cases and 15,000 deaths annually. About one-third of patients die and half of the survivors have severe neuropsychiatric sequelae. Most of China, South-east Asia and the Indian subcontinent are affected by the virus, which is spreading at an alarming rate. In these areas, wards full of children and young adults afflicted by Japanese encephalitis attest to its importance.

EPIDEMIOLOGY

Although Japanese encephalitis virus (JEV) is confined to East Asia, it is numerically the most important cause of encephalitis of man worldwide, with an estimated 50,000 cases and 10,000 deaths annually^{1,2}. Like many other flaviviruses, JEV is zoonotic. Transmission bird, pigs and other amplifying vertebrates occurs via culicine mosquitoes—*Culex tritaeniorhynchus* being the most important. Man is an incidental host, infected only when living in close proximity to this enzootic cycle. Mostly this occurs in rural areas where mosquitoes breed prolifically in flooded rice fields; however, urban cases have been reported. Serological evidence indicates that most infections of man are asymptomatic infection vary between one in 25 and one in 300³.

Over the last 50 years the epidemiology of JEV has changed. Although in Japan, Korea and China mass vaccination campaigns have been associated with a decrease in the number of cases, the geographical areas affected by JEV has expanded to include all of Southeast Asia, most of China and the Indian subcontinent. Cases have recently been reported from the Australian Torres Strait Islands. The reasons for the expansion are

incompletely understood, but increasing irrigation and animal husbandry are thought to be important⁴. Patterns of JEV transmission vary regionally within individual countries and from year to year.

Japanese encephalitis is mostly a disease of children and young adults. In northern Thailand the incidence has been estimated to be up to 40 per 100,000 for age five to 25, declining to almost zero for those over 35³. The prevalence of antibody to the virus rises with increasing age in inhabitants of endemic areas⁵. However, when epidemics first occur in new locations, adults are affected as well as children⁶.

VIROLOGY

In common with all flaviviruses, Japanese encephalitis virus has a small (50nm) lipoprotein envelope surrounding a nucleocapsid comprising of core protein and 11 kb single stranded RNA (3800 kD). At least five genotypes of Japanese encephalitis virus occur in Asia, which relate roughly to the geographical area of isolation⁷. The complete nucleotide sequence has been published and includes 5' and 3' untranslated region and a single open reading frame encoding gene to three structural protein [capsid protein (C) precursor to the membrane protein (M) and envelope protein (E)] and seven non-structural proteins.

The search for genetic determinants of virulence in animal models of flavivirus encephalitis has focused on the E protein⁸. This protein, of about 500 amino acid, is the major component of the surface projections of the virion. Eliciting neutralizing antibodies and protective immune responses in the host. It is thought to be the cell receptor binding protein and mediator of membrane fusion and cell entry. A highly sulphated heparin

sulphate molecule has recently been identified as the putative receptor of flavivirus cell entry. It is suggested that the E protein has a major role in determination of virulence and neuro-invasiveness⁹. Whether such differences are important in determination the clinical presentation of Japanese encephalitis virus in humans is unknown.

CLINICAL FEATURES

Patients with Japanese encephalitis typically present after a few days of non-specific febrile-illness, which may include coryza, diarrhea and rigors². This is followed by headache, vomiting and a reduced level of consciousness often heralded by a convulsion. In some patients, particularly older children and adults abnormal behavior may be the only presenting feature.

A proportion of patients make a rapid spontaneous recovery (so called abortive encephalitis). Others may present with aseptic meningitis and have no encephalopathic features. Convulsions occur often in Japanese encephalitis and have been reported in up to 85% of children and 10% of adults¹⁰. In some children a single convulsion is followed by a rapid recovery of consciousness, resulting in a clinical diagnosis of febrile convulsion. Generalized tonic-clonic seizures occur more often than focal motor seizures. Multiple or prolonged seizures and status epilepticus are associated with a poor outcome.

The classic description of Japanese encephalitis includes a dull flat mask-like facies with wide unblinking eyes, tremor, generalized hypertonia and cogwheel rigidity. Opisthotonus and rigidity spasms, particularly on stimulation, occur in about 15% of patients and are associated with a poor prognosis. Other extrapyramidal features include head nodding and pill rolling movements, opsoclonus myoclonus, choreoathetosis and bizarre facial grimacing and lip smacking¹¹.

Changes of respiratory patterns, flexor and extensor posturing and abnormalities of the papillary and oculocephalic reflexes are poor prognostic signs and may reflect encephalitis in the brainstem¹². However in some patients a clear rostrocaudal progression of brainstem signs, an association with high CSF opening pressures and a reversal of signs on aggressive management of raised intracranial pressure suggests that transtentorial herniation may also contribute.

Acute Flaccid Paralysis

Recently a subgroup of patients infected with Japanese encephalitis virus presented with a polio-

myelitis-like acute flaccid paralysis are reported¹³. 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 the arms and was usually asymmetric. Thirty percent 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. At follow-up (1-2 years later) there was persistent weakness and marked wasting in the affected limbs. Nerve conduction studies demonstrated markedly reduced motor amplitudes and EMG showed a chronic partial denervation, suggesting anterior horn cell damage¹³. Flaccid paralysis also occurs in comatose patients with "classic" Japanese encephalitis, being reported in 5-20%. Electrophysiological studies have confirmed anterior horn cell damage and MRI of the spinal cord showed abnormal spinal intensity on T2 weighted images. Occasionally respiratory muscle paralysis may be the presenting features.

Investigations

A peripheral neutrophil leukocytosis is seen in most patients and hyponatremia 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. Typically there is a moderate CSF pleocytosis of 10-100 cells/mm³, with predominant lymphocytes, mildly increased protein (50-200 mg%) and a normal glucose ratio. However, polymorphonuclear cells may predominate early in the disease or there may be no CSF pleocytosis¹⁴.

In about 50% of patients CT shows bilateral non-enhancing low density areas in one or more of the thalamus basal ganglia, midbrain, pons and medulla. Magnetic resonance imaging is more sensitive, typically demonstrating more extensive lesions (typically high signal intensity on T2 weighted images) of the thalamus, cerebral hemispheres and cerebellum. Thalamic lesions of mixed intensity may also be seen on T1 and T2 weighted scans suggesting hemorrhage¹⁵. Imaging studies may be useful in distinguishing Japanese from herpes simplex encephalitis, where the changes are characteristically frontotemporal. However, most reports are of scans performed late in the illness and the diagnostic value of scans performed early is unknown. Single photon emission tomography (SPECT) studies carried out acutely may show hyperperfusion in the thalamus and putamen. Follow-up studies have shown hypoperfusion in the same areas, as well as in the frontal lobes.

Various electroencephalographic abnormalities have been reported in Japanese encephalitis including theta and delta coma, burst suppression, epileptiform activity and occasionally alpha coma. Diffuse slowing may be useful in distinguishing Japanese encephalitis from herpes simplex virus, in which changes are characteristically frontotemporal.

Differential Diagnosis

Differential diagnosis of Japanese encephalitis is broad and includes other viral encephalitides (arboviruses, herpes viruses, enteroviruses and postinfectious and postvaccination encephalomyelitis), other CNS infections (bacterial and fungal meningitis, tuberculosis, cerebral malaria, leptospirosis, tetanus, abscess), other infectious diseases with CNS manifestations (typhoid encephalopathy, febrile convulsions) and non-infectious diseases (tumors, cerebrovascular accidents, Reye's syndrome, toxic and alcoholic encephalopathies, syndrome, toxic and alcoholic encephalopathies and epilepsy) (Table 1).

Outcome

About 30% of patients admitted to hospital with Japanese encephalitis die and around half of the survivors have severe neurological sequelae. However,

in areas with better hospital facilities there is a reduction in mortality, but a concomitant increase in the number of patients with sequelae². About 30% of survivors have frank motor deficits. These include a mixture of upper and lower motor neuron weakness and cerebellar and extrapyramidal signs¹⁶. Fixed flexion deformities of the arms and hyperextension of the legs with *equine feet* are common. Twenty percent of patients have severe cognitive and language impairment (most with motor impairment also) and 20% have further convulsions. A higher rate of sequelae is reported for children than adults. In addition, more detailed studies have shown that about half of those who were classed in the good recovery group have more subtle sequelae such as learning difficulties, behavioral problems and subtle neurological signs.

MANAGEMENT

Treatment for Japanese encephalitis is supportive and involves controlling convulsions and raised intracranial pressure when they occur. For many years corticosteroids were given, but a double blind randomized placebo controlled trial of dexamethasone failed to show any benefit. Careful nursing care and physiotherapy are needed to reduce the risk of bedsores, malnutrition and contractures. Aspiration pneumonia

Table 1: Differential diagnosis for patients with fever and neurological manifestations

Encephalitis due to arboviruses	Other CNS infections
Japanese encephalitis virus	Cerebral malaria
Dengue virus	Bacterial meningitis
Murray Valley encephalitis virus	Tuberculosis meningitis
West Nile virus	Cryptococcal meningitis
Banna virus	Brain abscess
Snowshoe hair virus	Leptospirosis
Me Tri virus	Rickettsioses
	HIV encephalopathy
	Guillain-Barré syndrome
Encephalitis due to other viruses	Other infectious disease with CNS manifestations
Herpes simplex virus	Viral illnesses with febrile convulsion
Enteroviruses—coxsackie, echo, polio viruses	Typhoid encephalopathy
Rabies virus	Confusional states associated with diarrhoea (shigella)
	Viral infections associated with swollen fontanelle
Postinfectious encephalitis (ADEM)	
Measles, varicella zoster	Non-infectious diseases
Mumps, rubella, Epstein-Barr virus	Tumours
Influenza, parainfluenza, <i>Mycoplasma</i>	Subarachnoid haemorrhage
Post-vaccine encephalitis	Cerebrovascular accidents
Semple rabies vaccine	Epilepsy
Measles vaccine	Reye's syndrome
	Other metabolic encephalopathies
	Hysteria

ADEM = Acute disseminated encephalomyelitis

is a common occurrence in patients with a reduced gag reflex. There is currently no specific treatment for Japanese encephalitis. Isoquinolone compounds are effective *in vitro* and monoclonal antibodies are apparently effective in animal models. Interferon- α is currently the most promising potential treatment. It is produced naturally in the CSF in response to infection with Japanese encephalitis virus and *in vitro* it has activity against the virus¹⁷. Recombinant interferon- α has been given in open trials to a few patients with encouraging results and is currently being assessed in a placebo controlled double blind trial¹⁸.

PREVENTION

Broadly speaking, measures to control Japanese encephalitis include those which interfere with the enzootic cycle of the virus and those which prevent disease in humans. Measures to control breeding of *Culex* mosquitoes, such as the application of larvicides to rice fields and insecticide spraying have proved ineffectual¹⁹. Inactivated and live attenuated vaccines (described below) have been used to protect swine against the virus; however, widespread vaccination is not feasible in most setting. Residents and travellers to endemic areas should take personal protection to reduce the number of *Culex* bites. These include minimising outdoor exposure at dusk and dawn, wearing clothing that leaves a minimum of exposed skin, using insect repellents containing at least 30% DEET (N, N-diethyl-3 methylbenzamide) and sleeping under bed nets. While these measure may be possible for the short-term visitor, most are not practical for residents of endemic areas.

Formalin Inactivated Vaccine

Formalin inactivated vaccines against Japanese encephalitis were produced in different countries including India⁵. Two doses of vaccine are required to give protective antibody levels to suitable high number of recipients (80 to 100%). It is given at 0 and 7 days, with booster immunization recommended at 1 year.

Adverse Reactions

Japanese encephalitis vaccination is associated with a moderate frequency of local and mild systemic side effects. Tenderness, redness and swelling has been reported in up to 20% of vaccine recipients and fever, headache, malaise and chills have been reported in about 10%. Because the vaccine is derived from mouse brain there has been concern about neurologically related side

effects, though they are rare. Urticaria has been reported in some recipients.

Live Attenuated Vaccine

In 1988, the Chinese authorities licensed a new live attenuated Japanese encephalitis vaccine. This strain (SA 14-14-2) was produced by passing the virus through weanling mice, then culturing in primary baby hamster kidney cells. The vaccine has been shown to be safe and immunogenic and has been given to over 100 million children in China. Its efficacy was recently demonstrated in a relatively simple and inexpensive case-control study in which the prevalence of immunization was compared between 56 cases of Japanese encephalitis and 1299 age and village matched controls²⁰. The effectiveness of one dose was 80% (95% confidence intervals 44-93%) and of two doses 1 year apart 97.5% (86-99.6%). The vaccine's short-term safety was recently confirmed in a randomized trial of 26,000 children and it has been shown to be immunogenic at the shorter dosage interval of 1 and 2.5 months, which might facilitate its incorporation into existing immunization programs²¹.

FUTURE DIRECTIONS

Despite some success with formalin inactivated vaccination and the promise of the new live attenuated vaccine, Japanese encephalitis looks likely to remain an important public health problem into the next millennium. Unlike smallpox and polio, for which humans are the only host and elimination by vaccination is feasible, the enzootic nature of Japanese encephalitis virus means that there is no possibility of global eradication. The geographical area affected is expanding and the 2.8 billion people living in affected areas will continue to be exposed to the virus. Thankfully, only a small proportion of them develops disease, but we have little understanding of what determines who develops disease and how it will manifest.

Considering the many cases of Japanese encephalitis, research into antiviral drug has been relatively neglected. Interferon- α , which was shown to be effective *in vitro* and in animal models nearly 15 years ago is only now being assessed in human disease. Attention should focus on newer antiviral drugs and their possible role in Japanese encephalitis. Japanese encephalitis virus is expanding across the globe at an alarming rate. New rapid diagnostic methods should facilitate monitoring the spread of the disease in locations where, until now, the etiology of encephalitis could only be guessed. The environmental and ecological factors responsible for this

expansion need further investigations, with a view to control the spread of this fascinating and devastating disease.

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