Japanese encephalitis

Japanese encephalitis

Summary

- Flavivirus, belongs to JEV serogroup
- Vector: mosquito, Culex species
- Main clinical presentation: Febrile disease, neurological syndrome (FD, NS)
- Vaccine available.

Virus

JEV is the prototype virus of the JE serogroup Flaviviruses, which also includes several medically important etiological agents of encephalitis (see below). Taxonomically, JEV is closely related to other clinically important flaviviruses, including yellow fever virus (YFV), dengue virus, and tick-borne encephalitis virus. Like all flaviviruses, JEV is a small enveloped virus, with a single-stranded positive-sense RNA genome. The genome encodes a single long open reading frame (ORF) flanked by 2 short non-coding regions (NCRs) at the 5′ and 3′ ends.

The Japanese encephalitis serological group of flaviviruses counts 8 virus species and 2 subtype viruses with an extensive geographic distribution (Figure 11):

Japanese encephalitis virus (JEV) in South-east Asia, Papua New Guinea and the Torres Strait of northern Australia.

West Nile virus (WNV) in Africa, southern and central Europe, India, the Middle East and North America.

Kunjin virus (a subtype ofWNV) in Australia and Papua New Guinea.

Murray Valley encephalitis virus (MVEV) in Australia, Papua New Guinea and the western Indonesian archipelago

St. Louis encephalitis virus (SLEV) in North and South America.

Other minor members of the group are Usutu (USUV), Koutango and Yaounde viruses in Africa; Cacipacore virus in South America; and Alfuy, a subtype of MVEV, in Australia. Most members have

avian vertebrate hosts and are vectored primarily by Culex spp. mosquitoes.

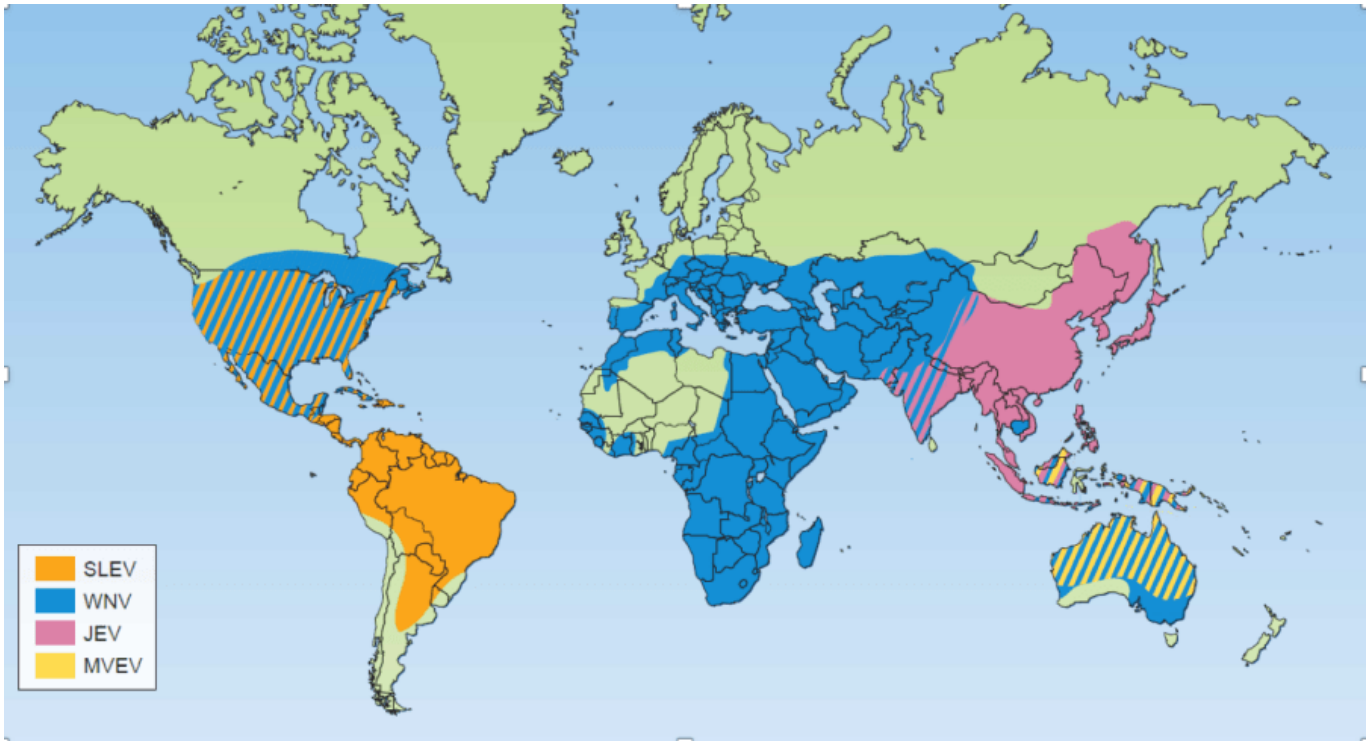

Figure 11 Global distribution of Japanese Encephalitis serogroup flaviviruses (Mackenzie et al, Nat Med)

Transmission

JEV is the most important cause of viral encephalitis SEA, with 30,000–50,000 cases reported annually, although this may be a considerable underestimate because of inadequate surveillance and reporting. JEV is amplified in an enzootic cycle that involves mosquito vectors (mainly Culex species) and vertebrate hosts (primarily pigs and birds) (Figure 12). JEV is occasionally transmitted to dead-end hosts, such as humans and horses.

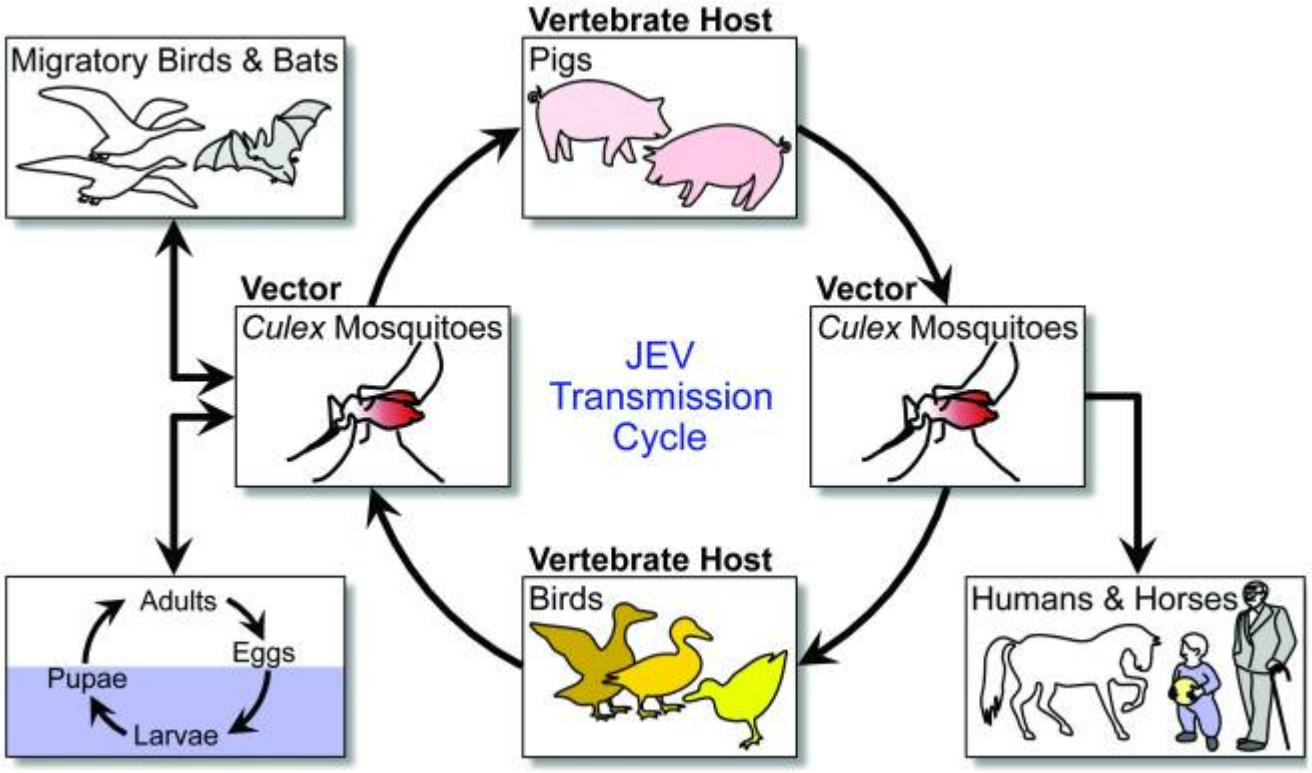

Figure 212Japanese Encephalitis virus- Transmission cycle (Yun S-I *et al*, Hum Vaccin Immunother)

Clinical features

The incubation period for JEV is 5-15 days. Most infections remain asymptomatic, with estimates of the ratio of symptomatic to asymptomatic infection from 1 in 25 or lower. Sero-surveys in JEV endemic areas have shown that the majority of adults have been exposed to JEV. As with other flaviviruses, the determinants of clinical disease manifestation are ill understood, but are likely to include endemicity, exposure to mosquitoes, pre-existing antibodies to flaviviruses and virus strain differences. Clinical disease often starts with unspecific febrile illness. In neuroinvasive JEV infections, patients usually seek consultation a couple of days after a prodromal syndrome, when meningeal irritation, headache, stupor, coma and convulsions occur. Classical description of Japanese encephalitis includes a Parkinsonian syndrome with a mask-like face, wide unblinking eyes, tremor, generalized hypertonia, cogwheel rigidity and other abnormalities of movement. Along with upper motor neuron signs, cerebellar signs and cranial nerve palsies may occur. Paralysis of the upper extremities is more common than that of the legs. Persistent motor deficits are common (30%), as are severe cognitive and language impairment (20%).

When performing lumbar puncture, 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 (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 pleocytosis.

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 haemorrhage.

Encephalitis has a high mortality rate (25-30%). Pregnant women are at risk of intra-uterine infection and death of the foetus during the first two trimesters.

Diagnosis

Anti-JEV immunoglobulin M (IgM) is produced soon after infection and is detectable in 90% of cases in cerebrospinal fluid (CSF) by 4 days and in serum by 7–9 days following the development of clinical illness. Anti-JEV IgM is less cross-reactive and therefore more specific than IgG. WHO recommends JEV-specific IgM antibody capture ELISA (MAC ELISA) as the first-line serological assay to diagnose acute JEV infection. However Serology MAC ELISA underestimates recent infection with Japanese encephalitis virus, in comparison to real time reverse transcriptase PCR[50].

The diagnosis can be made by isolating the virus from the cerebrospinal fluid early in the disease or by serology, but it is not a sensitive method of laboratory diagnosis in clinical specimens because the low-level transient viremia is cleared soon after onset of illness.

Treatment

As with other flaviviruses, treatment for Japanese encephalitis is supportive. Convulsions and raised intracranial pressure should be treated when they occur. Randomized controlled trials failed to show benefit for the use of corticosteroids, interferon-alfa-2a or ribavirin. Intravenous Immunoglobulins (IVIG) produced in countries where flaviviruses are endemic contains high titres of specific neutralizing antibody, because most of the population have been exposed to the virus. A recent pilot study (2016) cleared the way for a phase III trial of treatment of JEV with IVIG in Nepal.

Prevention

Given its endozootic life cycle JEV cannot be eradicated. In absence of effective antiviral therapy, vaccination is the most important tool to control human JEV infections.

Vaccination

Four different vaccines are available, but all induce only short-term immunity. The vaccine IXIARO® (2 injections, on day 1 & 28) is approved in Europe for people aged 18 years and older. Indications for vaccination in travellers include people who travel at least 3-4 weeks in a rural endemic area or who intend to live in these areas for longer periods even in an urban environment. After a 2-dose primary immunization schedule (0-28 days), the seroprotection rate declines from 8% at 1 month to 48% at 24 months but reconversion is complete with a booster after 1 or 2 years. In older people the vaccine can be given safely, but a 3rd dose may be needed at primary immunization.

Vector control

In addition to vaccination, Japanese Encephalitis can be prevented by vector control measures, see also general section.

LAST UPDATED BY ADMIN ON JULY 14TH, 2022