Japanese Encephalitis and Japanese Encephalitis Vaccination

Synonyms: Japanese B encephalitis, JE

This is a notifiable disease in the UK (other than Scotland). See the
The infection is caused by a flavivirus, a single-stranded RNA virus. It is transmitted by the bite of the Culex tritaeniorhynchus mosquito. The virus multiplies at the site of the bite and in regional lymph nodes before viraemia develops. Viraemia can lead to inflammatory changes in the heart, lungs, liver and reticuloendothelial system.

The immune system usually overwhelms the virus before it can invade the central nervous system and so most disease is subclinical. Neurological infection is thought to occur in only about 1 case in 250. The virus can spread across vascular endothelial cells, with involvement of large areas of the brain, including the thalamus, basal ganglia, brainstem, cerebellum, hippocampus and cerebral cortex.

Epidemiology\[1, 2, 3\]

- Japanese encephalitis (JE) is the most important cause of viral encephalitis in Asia.
- The endemic area for JE spreads across Asia from Pakistan to the coast of Siberia and includes Japan. Around 3 billion people live in this endemic area across 24 countries. China accounts for around 50% of cases.\[4\]
- In temperate parts it is a seasonal disease, from June to September but further south in subtropical areas, transmission begins as early as March and extends until October. In some tropical areas such as Indonesia, Malaysia and the Philippines, infection occurs all year round.
- The transmission cycle involves mosquitoes, pigs and/or wading birds. (Humans, once infected, do not transmit the virus back to feeding mosquitoes or other humans.) It therefore tends to occur in rice fields where wading birds are found or in areas of pig farming.
- There are around 68,000 clinical cases of JE each year.
- 75% of cases occur in children aged under 14 years. This age distribution applies to the indigenous population. Visitors may be affected at any age.
- The risk to people from non-endemic areas travelling to Asia is around 1 case per 1 million travellers.
- Japanese encephalitis is rare in the UK and contracted abroad. There have only been 2 cases documented in travellers from the UK.\[5\]

Presentation

- The incubation period is 5 to 15 days.
- The majority of cases are asymptomatic.
- Around 1 in 250 infections are estimated to become clinically apparent.
- There is a prodrome of fever, headache, nausea, diarrhoea, vomiting and myalgia, which may last for several days.
- This may be followed by a spectrum of neurological disease, ranging from mild confusion, to agitation, to overt coma.
- Two thirds of patients have seizures. It is more common in children, while headache and meningism are more common in adults.
- Tremor or other involuntary movements are common.
- Mutism has been described as a presenting symptom, as has a syndrome of acute flaccid paralysis.
- Fever resolves by the second week and choreoathetosis or extrapyramidal symptoms develop as the other neurological symptoms disappear.
Neurological features
These are varied and may include:

- Generalised weakness, hypertonia and hyperreflexia, which are common.
- Papilloedema (seen in a minority).
- Cranial nerve findings such as disconjugate gaze and cranial nerve palsies.
- Extrapyramidal signs. They include a mask-like face, tremor, rigidity and choreoathetoid movements, producing a Parkinson's-like syndrome.
- Central hyperpnoeic breathing.

Differential diagnosis

- Meningitis.
- Dengue fever and other flaviviruses.
- Malaria.
- Herpes simplex encephalitis.

Investigations

- Blood tests: there may be a mild, nonspecific leukocytosis in the first week. Inappropriate ADH secretion may result in hyponatraemia.
- The JE virus can occasionally be isolated from the blood during the first week of illness. The CSF rarely yields virus, except in severe or fatal cases.
- CT or MRI scan may show bilateral thalamic lesions with haemorrhage. The basal ganglia, putamen, pons, spinal cord and cerebellum may also be abnormal. MRI is more sensitive and may help differentiate from other causes of encephalitis.\[6\]
- Lumbar puncture may be undertaken. This may be undertaken to exclude meningitis or other causes of encephalitis. CSF is the preferred sample for antibody testing, as a positive test confirms the virus has entered the central nervous system.

Antibody tests\[7\]

- IgM capture enzyme-linked immunosorbent assay (ELISA) of serum or CSF is the standard diagnostic test. Sensitivity is nearly 100% when both serum and CSF are tested.
- Virus-specific IgM antibodies are detectable 3-8 days after the onset of illness and persist for 30-90 days. A positive result may reflect vaccination or immunity from past exposure.
- There is some cross-reactivity with other flaviviruses and from Japanese encephalitis and yellow fever vaccinations.
- Newer IgM dot ELISA for CSF and serum are portable and simple tests that can be used in the field. Compared with IgM capture ELISA as the gold standard, the sensitivity and specificity are around 98% and 99% respectively.

Management

- There is no specific treatment for the disease and management is purely supportive.\[8\]
- Support often includes feeding, airway management, and anticonvulsants.
- Outcome appears to be improved by adequate sedation, fluids and management of sodium.

Complications

- As well as problems such as pneumonia and urinary tract infection, there are potential complications of convulsions.
- Neurological complications may not resolve when the disease subsides. 30-50% of survivors have significant neurological problems.\[2\]
Prognosis

- The prognosis is highly variable and neurological deficits are common.
- 20-30% of severe cases are fatal.\(^5\)
- Disabilities may range from subtle changes in behaviour to blindness, ataxia, weakness and movement disorders.

Prevention

The pivots of prevention are:

- Avoidance of mosquito bites.
- Vector control.
- Vaccination.

**Avoidance of mosquito bites**

Mosquitoes tend to bite at night and for visitors to endemic areas the usual precautions are recommended. This may mean using insect repellent after dark, wearing long sleeves and covering legs and avoiding sitting near lights unless behind mosquito screens. The use of mosquito nets at night should be considered as for malaria. Nets impregnated with insecticide or repellent are more effective.

**Vector control**

Vector control may include spraying insecticide, intermittent irrigation strategies, draining swamps and the introduction of fish that eat the larvae of the mosquito. In a substantial part of the area affected, the staple diet is rice, and paddy fields are an essential part of the economy. Resistance to insecticides has increased.

Vector control is more likely to result in eradication or reduction of the disease than human vaccination, because humans do not spread the disease onwards. Newer biocontrol methods have shown some promise.\(^9\)

**Vaccination\(^{10}\)**

Although there are a number of vaccines in use worldwide, in the UK the only licensed vaccine is Ixiaro®. The primary course is two doses 28 days apart, given intramuscularly, other than for those with bleeding disorders in whom it is given subcutaneously. The Green Cross vaccine is no longer recommended in the UK as there is a licensed option available.

**Dose**

- For children between the ages of 2 months and less than 36 months: 0.25 ml at 0 and 28 days.
- For children ≥3 years of age, and adults: 0.5 ml at 0 and 28 days.
- A booster may be given at 12-24 months for those at ongoing exposure.

**Indications**

JE vaccination is recommended for:

- Those going to reside in endemic/epidemic areas.
- Travellers to endemic areas if:
  - Staying a month or more in the transmission season.
  - At increased risk due to nature of activity (eg, spending time in paddy fields or pig farms).
- Laboratory staff with potential exposure to the virus.

**Contra-indications**

- Confirmed anaphylactic or severe reaction to vaccine or its components.
- Pregnancy or breast-feeding (balance risk of exposure against theoretical risk in pregnancy).

**Adverse reactions**
Common reactions include:

- Pain and tenderness at the site of injection.
- Headache.
- Myalgia.

Less common reactions include:

- Erythema, swelling, itching or hardening at the site of injection.
- Influenza-like illness.
- Fever.
- Fatigue.

Further reading & references

2. Japanese encephalitis Fact Sheet; World Health Organization, March 2014
5. Japanese Encephalitis - Travel Health Information Sheet; National Travel Health Network and Centre (NaTHNac), December 2013

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