

## SHORT REPORT

## Acute disseminated encephalomyelitis after treatment with Japanese B encephalitis vaccine (Nakayama-Yoken and Beijing strains)

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### Abstract

**Seven children with acute disseminated encephalomyelitis (ADEM) after treatment with Japanese B encephalitis vaccine (JBEV) (Nakayama-Yoken strain 1968-88 and Beijing strain 1989-93) were identified by mailed questionnaires and by compilation of previously published case reports. It was considered that encephalomyelitis might have been related to vaccine treatment as the vaccine is derived from mouse brain tissue infected with Japanese B encephalitis virus, a potentially cross reactive antigen. The incidence of severe neurological complications associated with the newer Japanese B encephalitis Beijing strain vaccine seemed to be less than one case per 1 000 000, which is similar to the incidence of neurological complications associated with the older Nakayama-Yoken strain vaccine.**

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Keywords: acute disseminated encephalomyelitis; Japanese B encephalitis vaccine

Encephalitis due to Japanese B virus is one of the most common causes of epidemic viral encephalitis in the world. It occurs in annual epidemics in Asia, affecting residents and travellers to the region. The disease is often fatal or crippling.<sup>1</sup> Beginning in 1989, Japanese B encephalitis vaccine (JBEV) was derived from Beijing strain antigens<sup>2</sup> rather than the Nakayama-Yoken strain that had been used since 1954.<sup>3</sup> Because of occasional cases of Japanese encephalitis among travellers, the US Public Health Service obtained an investigational new drug exemption (IND 1824).<sup>4</sup> Although there have been no studies of the neurological complications of JBEV in Japan since that by Okinaka *et al.*<sup>5</sup> in 1967, case reports of acute disseminated encephalomyelitis (ADEM) after JBEV have been reported by Matsukura *et al.*,<sup>6</sup> Kanesaki *et al.*,<sup>7</sup> and Ohtaki *et al.*<sup>8</sup> We identified cases by mailed questionnaires and collected the previous reports of neurological complications

due to JBEV Beijing and Nakayama-Yoken strains in an effort to update the study by Okinaka *et al.*<sup>5</sup>

### Patients and methods

The questionnaire was intended to screen for potential patients with neurological complications after treatment with JBEV. Forms were mailed to 162 medical institutions including paediatric departments in medical colleges, schools of medicine, children's hospitals, and rehabilitation facilities for children, all facilities that might be served by paediatric neurologists. Acute disseminated encephalomyelitis was defined, for the purposes of the questionnaire, as an acute inflammatory disease with perivenous lymphocytic infiltration and scattered demyelinating foci in the white matter of the CNS. The presence of characteristic CNS lesions was confirmed by CT or MRI. The symptoms of ADEM must have appeared abruptly within one month after vaccination. Other similar neurological conditions must have been ruled out. We also identified cases of neurological complications associated with JBEV from the Japanese and English medical literature.

### Results

Results from the 120 returned questionnaires (reply rate 74%), combined with a review of previous reports identified seven children with ADEM after treatment with JBEV (table). Other neurological complications associated with the Japanese B vaccine included two patients with encephalitis (one having received the Nakayama-Yoken and the other the Beijing strain vaccine), one patient with encephalopathy after the Beijing vaccine, one patient with transient hemiplegia after the Beijing vaccine, and three patients with aseptic meningitis after the Nakayama-Yoken vaccine.

### Discussion

Japanese B encephalitis is an important public health concern not only in Japan but also in other parts of east Asia.<sup>1</sup> Japanese B

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## Seven patients with acute disseminated encephalomyelitis after treatment with Japanese B encephalitis vaccine

Patient	Age/sex	Type of strain	Date of inoculation	Date of onset	Symptoms at onset	Neurological sequelae
1	1/F	N-Y	6 July 1968	11 July	Fever, convulsion, somnolence	MR, epilepsy. Hemiplegia.
2	6/M	N-Y	21 June 1978	30 June	Fever, somnolence, gait disturbance	None
3	7/F	N-Y	Unknown 1979	2 days after vaccination	Fever, diplopia, gait disturbance. Urinary incontinence	None
4	7/F	N-Y	14 July 1987	27 July	Somnolence, convulsion, cranial nerve palsy (III, IV, VI), cerebellar ataxia	None
5	3/F	B	13, 20 June 1989	21 June	Fever, convulsion, gait disturbance, urinary incontinence (MBP 8.5 ng/ml)	None
6	6/F	B	25 June, 7 July 1989	21 July	Impaired vision, fever, somnolence, meningeal sign, gait disturbance, urinary incontinence	None
7	5/M	B	30 May 1990	16 June	Fever, meningeal signs, urinary incontinence, gait disturbance (MBP 18.5 ng/ml)	None

M=male; F = female; N-Y = Nakayama-Yoken strain; B = Beijing strain; MBP = myelin basic protein in CSF (normal < 4.0 ng/ml); MR = mental retardation.

encephalitis vaccine derived from the Nakayama-Yoken strain of the virus was developed in 1954.<sup>2,4</sup> A highly purified vaccine derived from the Beijing-1 strain was developed in 1989.<sup>2</sup> The annual incidence of Japanese B encephalitis was decreased greatly to less than 60 cases per year between 1980 and 1993.<sup>9</sup> The efficacy of vaccination was shown in the northern Thai Province in 1988.<sup>1</sup> Because the JBEV contains material from infected mouse brain, postvaccination ADEM might occur as the result of an immune mediated process. Acute disseminated encephalomyelitis has been reported to occasionally occur about one month after vaccination.<sup>10</sup> The differential diagnosis of acute encephalopathy includes viral encephalitis, multiple sclerosis, progressive multifocal leukoencephalopathy, cerebrovascular disorders, leukodystrophy, and other neurological disorders. The observed clinical course, appropriate viral titres, findings in CSF, electroencephalography, and MRI findings are useful for differentiating these diseases. A raised myelin basic protein concentration in the CSF is especially suggestive of ADEM. We hypothesised that inoculation with JBEV might lead directly to the development of this disorder. Other potential neurological complications, such as aseptic meningitis, encephalitis, encephalopathy, and transient hemiplegia have shown no correlation with the current version of the vaccine.

About 60% of school aged children in Japan receive JBEV every year.<sup>11</sup>

The incidence of neurological complications associated with the Beijing strain derived vaccine is likely less than 1 per 1 000 000,<sup>12</sup> even if one assumes that other neurological complications associated with the vaccine equal those associated with the

older Nakayama-Yoken derived vaccine. We conclude that the JBEV is safe but that neurological complications, especially ADEM, may occasionally occur within one month of treatment.

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