Long-Term Disability from Acute Childhood Japanese Encephalitis in Shanghai, China

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Abstract. We traced 85 Japanese encephalitis (JE) patients, 6–27 years after hospitalizations. The first control group was made up of 73 non-JE encephalitis patients 6–27 years previously, whereas the second control group was made up 78 neighborhood residents, matched to the 78 surviving JE cases by age, sex, and residence. All subjects were examined with neurologic examinations, intelligence quotient (IQ) measurement, Mini-Mental State Examinations (MMSE), and activities of daily living (ADL) assessments. At follow-up, 22% of JE patients had objective neurologic deficits compared with 3% of non-JE encephalitis patients. Moreover, 28% of JE patients had subnormal IQs, as opposed to 2% non-JE encephalitis patients. Abnormal ADL scores were only noted in 15% JE patients. All neighborhood controls had normal examination results, and one non-JE encephalitis case showed mildly reduced IQ. The study showed that significant neurologic and overall functional disability were evident in a high proportion of JE survivors many years after their index hospitalizations.

INTRODUCTION

Japanese encephalitis (JE), a mosquito-borne viral disease, is endemic in virtually all countries of Asia. The disease is fatal in 10–30% of patients and a significant proportion of survivors exhibit neurologic disability such as impaired cognition, seizures, motor impairment, coordination dysfunction, and mental disorders.1–16 With the near elimination of poliomyelitis, JE has become the most important neurologic infection among Asian children.

Long-term disability is an important component of the JE disease burden. Such disease burden cannot be fully estimated by short-term follow-up studies because some neurologic disorders resolve over time and others appear at varying intervals after the acute illness.1 Studies with suitably long periods of follow-up are lacking, and past studies of this topic have not been properly controlled or observer-blinded. Here we describe a controlled, blinded assessment of long-term neurologic disability in persons who acquired JE 6–27 years earlier in Shanghai, China.

MATERIALS AND METHODS

Our study entailed two comparisons. In the first, we compared neurologic disability in cohorts of persons who had had JE (JE group) with that in persons who had had acute encephalitis with negative tests for JE (non-JE group). In the second cross-sectional comparison, we contrasted neurologic disability in the JE group with contemporaneous neighborhood controls. All subjects were examined for neurologic and functional deficits. The study received ethical clearance from Institutional Review Boards of the Program for Appropriate Technology in Health, Seattle, WA, and the Hua-shan Hospital, Shanghai, China. Written informed consent was obtained from all study subjects or their guardians.

JE and non-JE study subjects. In all, we identified 329 persons (study subjects) who had been hospitalized when < 15 years old (1973–1994) for putative JE, in one of two major Shanghai pediatric hospitals (Shanghai Children’s Hospital and Shanghai Medical University-affiliated Pediatric Hospital). These subjects had been discharged alive. We reclassified these patients as JE or non-JE based on whether laboratory results in the index hospitalizations fulfilled certain criteria (vide infra). These two groups constituted historic cohorts that were examined and compared in 2000 for neurologic disability.

Collection and interpretation of hospitalization data. Hospital records were evaluated of encephalitis cases. The records were scrutinized to obtain demographic and clinical data. Because of the diagnostic fashion at the time, irrespective of laboratory test results, all subjects in the two cohorts had received clinical diagnoses of JE at discharge on the basis of seasonal occurrence and clinical manifestations of acute encephalitis.17

For this study, we examined the laboratory results during the hospitalizations to reclassify patients as either JE or non-JE (all surviving patients with discharge diagnoses of JE had had one or more immunoassays done on serum obtained during their hospitalizations). Before 1990, complement fixation (CF) and hemagglutination inhibition assays (HIA) were used for laboratory diagnosis in the two study hospitals. After 1990, IgM-capture enzyme-linked immunosorbent assay (ELISA) became the standard. We reclassified a patient’s illness as JE if acute or convalescent serologic assays showed 1) HI antibody titer ≥ 1:80,18,19 2) CF antibody titer ≥ 1:4,18 or 3) positive results in the IgM-capture ELISA. These diagnostic criteria were formulated before the study.18,19 Although these criteria do not discriminate JE from other flavivirus infections with complete accuracy, we judged the criteria to be sufficient because neither dengue fever nor West Nile virus has been observed in Shanghai.20

In all, 93% of the study subjects were tested by CF, whereas 4% and 3% cases were tested by IgM-capture ELISA and HIA, respectively. Overall, 160 of the 329 study subjects were defined as JE and 169 cases were defined as post-non-JE; of the non-JE cases, 92% had no detectable CF antibody in both admission and discharge specimens. In the course of assembling these 329 survivors of encephalitis classified clinically as post-JE, we discovered an additional 15 cases who died dur-
ing the index hospitalizations for putative JE. Five tested positive for JE and five tested negative. The remaining five died before serologic specimens were obtained. Because the patients and their families were unaware of these reclassified diagnoses and because the JE patients were contemporaneous with the non-JE patients, the non-JE group served as a useful control group for follow-up assessments of the prevalence of neurologic disability attributable to JE.

Assembly of neighborhood controls. Because the non-JE hospital controls consisted of persons who had had acute encephalitis and thereby might be expected to have long-term neurologic sequelae, we also assembled a second control group from the general population. For this second set of controls, we selected one person, matched to each confirmed JE case by sex and age (+1 year) from the residence immediately to the right of the case residence. We excluded from this control group any subject with a history of an acute neurologic illness. If an eligible consenting subject was not available next door, we searched consecutive residences to the right of the case residence until one eligible consenting subject was identified. No subjects had to be excluded because of past neurologic events, and all subjects approached for participation gave their consent.

Follow-up of subjects. The follow-up of study subjects from the three groups was done in 2000. To assemble patients who had earlier survived encephalitis (JE or non-JE), we attempted appointments at the Huashan Hospital clinics. Home interviews were made if the patients did not come to the appointments. We used the registered permanent residence records of the Shanghai Police Bureau to search for patients who could not be contacted by home visit or by postal communication.

After efforts to trace the discharged patients, we located 185 of the 329 subjects or their guardians, and 158 agreed to participate in the study and signed informed consent forms. Of these 158 subjects, 85 (78 alive, 7 died after discharge) had confirmed JE and 73 (71 alive, 2 died after discharge) had non-JE encephalitis (Figure 1).

Each subject was examined at follow-up. Subjects who had encephalitis were examined by neurologists blinded to the laboratory criteria for the diagnosis of JE and to the specific laboratory test results from the index hospitalizations for patients in the two post-encephalitis groups. Blinding was further enhanced by the fact that all patients in these two groups had been given the clinical diagnosis of JE at discharge and this diagnosis was indicated in the medical records. Neurologists completed neurologic and cognitive examinations either at Huashan Hospital clinics or, when this was not feasible, at patients’ homes. The general population controls had identical examinations. The diagnoses of neurologic disorders were made by neurologists on the basis of the results of clinical and laboratory examinations.

Structured neurologic examinations included evaluation of seizures, speech, autonomic nerve function, cranial nerve function, motor and sensory functions, and reflexes. Intelligence Quotient (IQ) measurement and Mini-Mental State Examination (MMSE) were used for intelligence evaluation. We evaluated children aged 6–16 years with the Wechsler Intelligence Scale for Children (WISC) and used the Wechsler Adult Intelligence Scale (WAIS) for subjects 17 years and older. Adults were tested with an urban or a rural version of test according to their residence location. Both of these tests have been adapted for use among Chinese populations. A proportion of patients refused IQ testing, which took 2 or more hours.

Definitions of endpoints. Neurologic disability was defined as any abnormal finding on structured neurologic examination. IQ scores of 70–84 were classified as mildly abnormal.

![Figure 1](image-url)
(> 1 but < 2 SE below normal range) and those < 70 (> 2 SE of normal range) were considered severely abnormal. An MMSE score < 21 was regarded as abnormal. For the activities of daily living (ADL) scale, an assessment of overall functioning that considers 20 basic functions of daily activities, moderate and severe disabilities were categorized by scores of 21–60 and 61–80, respectively.

Statistical analysis. Comparisons of the JE group with each of the two comparison groups for dimensional variables were evaluated with the Student t test or the Mann-Whitney U test when the data were not normally distributed. Those for dichotomous variables were assessed by χ² test or Fisher exact test when data were sparse. A χ² test for trend was used to test for trend in odds ratios among ordered categories. To compare dichotomous variables, after adjusting for confounding factors, we fitted multiple logistic regression models. For contrasts of the two post-encephalitic groups, we forced the following potential confounders into the models: age (years) at discharge, sex, years since the index hospitalization, and rural versus urban residence at the time of the index hospitalization. For comparisons of the JE group with the neighborhood control group, we controlled for age (years) at follow-up, sex, and rural versus urban residence at the time of follow-up. The coefficient for the variable for the group to which the subject belonged in these models was exponentiated to estimate the adjusted odds ratio for the association, and the SE for the coefficient was used to estimate the 95% confidence interval (CI) for the adjusted odds ratio. All P values and CIs were estimated in a two-tailed fashion. Differences were considered to be statistically significant at P < 0.05.

RESULTS

Comparison of baseline features of patients who were followed versus those lost to follow-up in the JE and non-JE groups. The baseline features were similar between those followed and those dropped out in both JE and non-JE groups (Table 1), although comparison of traced patients between the two groups revealed that more years had elapsed from the time of index hospitalization to follow-up for the JE than for the non-JE group (17.2 versus 14.5 years, P < 0.001), and more JE subjects than non-JE patients lived in rural areas (93% versus 45%, P < 0.01) that is characteristic for a mosquito-borne disease such as JE (Table 1). Moreover, traced JE patients had been hospitalized significantly longer and had a higher proportion of neurologic deficits at discharge than the traced non-JE patients that indicates severer course of the disease for the JE than for the non-JE group (Table 1).

Neurologic findings for JE and non-JE groups and for neighborhood controls. Seven JE patients and two non-JE patients died after hospital discharge; all had neurologic deficits at discharge. For follow-up, we evaluated 78 JE patients, 71 non-JE patients, and 78 neighborhood controls. In all, 26 types of neurologic deficits were found in 17 (22%) of 78 JE patients (Table 2; Figure 2). Eight of the 17 had motor defects: 4 with paralysis, 2 with hemiplegia, and 1 each with monoplegia or chorea. Six of these eight had aphasias combined with motor deficits. These deficits were evident at discharge from the index hospitalizations and showed no apparent improvement with time after discharge. In addition, 10 JE patients had seizures of diverse types: 9 with generalized tonic-clonic seizure (GTC) and 1 with focal seizure.

Neurologic deficits were milder and less frequent in the non-JE group: only two cases with focal seizure were found (Figure 2), both appearing after discharge. Another two patients who had motor deficit during hospitalization recovered after discharge and were normal at follow-up examinations. The odds ratio for the presence of at least one neurologic deficit in the JE versus non-JE groups, adjusted for age, sex, residence, and years elapsed since index hospitalization, was 6.30 (95% CI: 1.24–31.91, P < 0.05). None of neighborhood controls exhibited a neurologic abnormality on physical examination (Table 2).

Neurologic abnormalities such as muscular rigidity and motor weakness, evident at discharge, had resolved in 11 JE cases (13%) at the time of follow-up. On the other hand, eight (10%) JE patients developed seizure disorders 3 to 17 years after discharge; another two (3%) JE patients showed dysfunction of autonomic nerve or optic atrophy at the follow-up examination that had not been noted on examinations during index hospitalizations. A total of 10 patients with seizure disorders were found in the JE group compared with 2 in the non-JE group (Figure 2). The odds ratio of having a seizure disorder in JE versus non-JE patients, adjusted for age, sex, years of follow-up, and residence, was 3.03 (95% CI: 0.52–17.76).

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Comparison of features between JE and non-JE patients and between those followed up and those lost to follow-up</td>
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<tr>
<th></th>
<th>JE Followed up (N = 88)</th>
<th>JE Not followed up (N = 75)</th>
<th>P value</th>
<th>Non-JE encephalitis Followed up (N = 73)</th>
<th>Non-JE encephalitis Not followed up (N = 96)</th>
<th>P value for followed JE vs. followed non-JE encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>52 (61.2)</td>
<td>54 (72.0)</td>
<td>0.149</td>
<td>45 (61.6)</td>
<td>62 (64.6)</td>
<td>0.694</td>
</tr>
<tr>
<td>Age (years)</td>
<td>3.7 ± 2.6</td>
<td>3.5 ± 2.8</td>
<td>0.640</td>
<td>4.5 ± 3.1</td>
<td>4.7 ± 3.2</td>
<td>0.684</td>
</tr>
<tr>
<td>Resides in rural area (%)</td>
<td>79 (92.9)</td>
<td>58 (77.3)</td>
<td>0.005</td>
<td>33 (45.2)</td>
<td>43 (44.8)</td>
<td>0.957</td>
</tr>
<tr>
<td>Hospitalization days (mean ± SD)</td>
<td>25.9 ± 20.6</td>
<td>24.8 ± 18.9</td>
<td>0.727</td>
<td>16.9 ± 6.2</td>
<td>17.1 ± 7.4</td>
<td>0.852</td>
</tr>
<tr>
<td>Neurologic abnormality at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes (%)</td>
<td>25 (29.4)</td>
<td>15 (20.0)</td>
<td>0.185</td>
<td>4 (5.5)</td>
<td>11 (11.5)</td>
<td>0.169</td>
</tr>
<tr>
<td>No (%)</td>
<td>60 (70.6)</td>
<td>59 (78.7)</td>
<td></td>
<td>69 (94.5)</td>
<td>84 (87.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td></td>
<td>0 (0)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Year of discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1979 (%)</td>
<td>21 (24.7)</td>
<td>25 (33.3)</td>
<td>0.007</td>
<td>8 (11.0)</td>
<td>24 (25.0)</td>
<td>0.060</td>
</tr>
<tr>
<td>1980–1989 (%)</td>
<td>61 (71.8)</td>
<td>44 (58.7)</td>
<td></td>
<td>60 (82.2)</td>
<td>68 (70.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>1990–1994 (%)</td>
<td>3 (3.5)</td>
<td>6 (8.0)</td>
<td></td>
<td>5 (6.8)</td>
<td>4 (4.2)</td>
<td></td>
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</table>

* Includes only patients with known neurologic status at discharge.
Neurologic deficits in JE and non-JE encephalitis cases followed the survivors of a major portion of the disease burden associated with JE. In addition, 11 patients were considered normal on the basis of laboratory assays. Wang and Chen followed 54 of 77 serologically proved JE patients for 3–8 years after initial diagnosis. Of the 54, 23 (43%) exhibited neurologic sequelae, 24 (44%) showed psychiatric abnormalities, and 34 (63%) had mental deficit. However, the hospital in which the patients were seen cared for patients without sequelae at the 1-month point after JE diagnosis; patients without sequelae at the 1-month point were not included for follow-up. In 1957, Pieper and Kurland followed the survivors of a 1947 JE outbreak in Guam and found that 40% had neurologic sequelae; 11% were considered severe. However, in that study, only 13 JE patients were followed; another 14 JE patients had mumps encephalitis concurrent with JE infection. In addition, 11 patients were considered normal on the basis of correspondence without neuro-psychological evaluations.

In summary, these clinical reports disclose a wide range of outcomes. These may be attributed to design deficiencies, including a relatively short follow-up after JE diagnosis, small sample size, absence of a suitable comparison group, and selection bias.

Laboratory diagnosis of JE. CF antibody appears 1–2 weeks after the onset of JE; therefore, tests of both acute and

Cognitive function for the three groups at follow-up. In all, 78 JE patients, 71 non-JE encephalitis patients, and 78 neighborhood controls were evaluated by the MMSE. Eight (10%) JE patients and one (1%) non-JE patient had an MMSE score < 21, whereas all members of neighborhood control group had normal MMSE scores. The differences between JE patients versus non-JE patients and between JE patients versus neighborhood controls were all statistically significant (Table 2).

IQ tests were administered to 60 (76%) JE patients, 53 (74%) non-JE encephalitis patients, and 67 (85%) neighborhood controls. Of those, 17 (28%) JE patients had IQ scores < 85, 11 (18%) had severe mental retardation with IQ scores < 70, and 6 (10%) had IQ scores of 70–84. Only one (2%) non-JE encephalitis patient had an abnormal IQ (IQ = 78), and only one (2%) neighborhood control had an abnormal IQ (IQ = 82; Table 2). All differences in the prevalence of low IQ scores between JE patients versus non-JE patients and between JE patients versus neighborhood controls were statistically significant (Table 2). IQ scores were significantly lower in the JE group than in the post non-JE group (P < 0.001) and in the neighborhood control group (P < 0.001; Table 2). The odds ratios of having a low IQ, adjusted for age, sex, years elapsed since index hospitalization, and residence were 20.72 (95% CI: 2.15–199.26; P < 0.01) for JE patients versus non-JE patients and 26.64 (95% CI: 3.40–208.97; P < 0.001) for JE patients versus neighborhood controls.

Overall function status by ADL score at follow-up. All 71 surviving non-JE patients and 78 neighborhood controls had normal ADL scores (Table 2). In contrast, only 66 (85%) JE patients had normal ADL scores (P < 0.01 versus post-non-JE; P < 0.001 versus neighborhood controls). Of importance, five (6%) JE patients had ADL scores indicative of near incapacitation.

DISCUSSION

Our results show that JE is associated with a high frequency of long-term disability as measured by neurologic deficits, subnormal intelligence, and deficits in overall levels of function in basic activities of daily living. These findings support the contention that long-term severe disability constitutes a major portion of the disease burden associated with JE.

Relation to other studies. Schneider et al reported the neurologic abnormalities in 37% of pediatric JE cases and 26% of adult cases after 1 year, and Hoke et al. reported abnormal neurologic status in 45% of patients 3 months after acute JE illness. No longer follow-up evaluations were done. Kumar et al. reported major neurologic sequelae in 46% of JE patients 12–18 months after discharge, but this rate was exaggerated because only 55 of 90 patients returned to the hospital for evaluation. Home visits were not done and the authors admitted that subjects without sequelae were less likely to return for follow-up.

Lin followed 50 JE cases in China for 5–8 years and compared them with 50 neighborhood control children. He found that 18% of the JE patients had low IQs. Unfortunately, the JE diagnosis in the study of Lin was not confirmed by laboratory assays.

Figure 2. Neurologic deficits in JE and non-JE encephalitis cases 6–27 years after index hospitalization compared with findings in normal controls.

Table 2

<table>
<thead>
<tr>
<th>Examination</th>
<th>JE (N = 78)</th>
<th>Post-JE encephalitis (N = 71)</th>
<th>Neighborhood control (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal neurologic findings (%)</td>
<td>17 (21.8)</td>
<td>2 (2.8)†</td>
<td>0 (0)‡</td>
</tr>
<tr>
<td>MMSE score &lt; 21 (%)</td>
<td>8 (10.3)</td>
<td>1 (1.4)†</td>
<td>0 (0)‡</td>
</tr>
<tr>
<td>IQ &gt; 84 (%)</td>
<td>43 (55.1)</td>
<td>52 (73.2)‡</td>
<td>66 (84.6)‡</td>
</tr>
<tr>
<td>70–84 (%)</td>
<td>6 (7.7)</td>
<td>1 (1.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>&lt; 70 (%)</td>
<td>11 (14.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ADL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 21 (%)</td>
<td>66 (84.6)</td>
<td>71 (100)†</td>
<td>78 (100)‡</td>
</tr>
<tr>
<td>21–60 (%)</td>
<td>7 (9.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
| 61–80 (%) | 5 (6.4) | 0 (0) | 0 (0)

*P < 0.05; †P < 0.01; ‡P < 0.001 for comparison of cited group with the JE group.
§MMSE. Mini-Mental State Examinations. IQ was determined for 60 JE and 55 post non-JE encephalitis patients and for 67 neighborhood controls.
convalescent sera are needed as the evidence for JE diagnosis. We cannot rule out JE from the non-JE encephalitis group since 8% of the CF-based non-JE diagnoses were based on negative test results from a single specimen. However, the negative CF results were obtained from both acute and convalescent specimens from the majority of non-JE cases. Therefore, the possibility of misclassification of JE as non-JE was low and this misclassification would have only minimized the differences in the outcomes of disability between JE and non-JE encephalitis groups and thus made the conclusions more conservative.

Positive HIA results could represent previous JE infection and could be false for determination of new JE infection. Among true JE patients, however, 80–100% had HIA antibody titers \( \geq 1:80 \).\(^{18,19}\) This cut-off titer was found in only 2% of rural healthy residents in Shanghai in the 1970s.\(^{19}\) Only 3% of our study subjects were diagnosed as JE or non-JE by HIA test. IgM capture ELISA is sensitive and specific for JE diagnosis; however, only 4% of our cases were diagnosed as JE or non-JE by the presence of IgM anti-JE in the sera because this test was introduced in Shanghai in 1990s.

**Potential limitations.** Despite efforts to capture both severe and mild subjects by home visits, we were able to follow only 48% of the discharged patients. Patients lost from the follow-up because they had changed their addresses during the recent 20 years. We tried to measure the bias because of the dropout by comparing the characteristics of those followed with those lost to follow-up and could not find any statistically significant difference (Table 1). To control for information bias in this observational study, we assembled a non-JE encephalitis group as a control for the JE group. Both groups were followed for neurologic and mental deficits in a double-blind fashion. Both groups had similar social-demographic characteristics and similar proportions of dropout, yet exhibited differences in the frequency and severity of neurologic abnormality (Tables 1 and 2). Undoubtedly, non-JE encephalitis patients could also have permanent sequelae.\(^{33–37}\) The etiology of non-JE encephalitis, however, remains unknown.

Of the groups that we reviewed, the JE patients had longer follow-up (17.2 years) than the non-JE encephalitis patients (14.5 years). The difference in length of follow-up alone may have led to the finding of more neurologic deficits for JE than for non-JE patients. Also, more JE patients than non-JE encephalitis patients lived in suburban areas. To adjust for these variables, we used logistic regression model to estimate the odds ratio of the long-term disability associated with JE; and the adjusted odds ratio for the presence of at least one neurologic deficit in the JE versus non-JE groups, was 6.30, and it was 20.72 for a low IQ. On the other hand, however, there were too few seizures and deaths occurring as new events during the JE period for a meaningful statistical analysis.

Another limitation of this study is that the disability reported here may have been incompletely ascertained; further neurologic dysfunction may occur later in subjects who were considered normal during this study period.

**Latency of deficits.** We found that seizures and optic atrophy appeared 3–17 years after recovery from the acute illness. This indicates the potential for considerable latency in the onset of JE-associated neurologic dysfunction. Generalized tonic-clonic seizure is seen mostly after acute encephalitis and can be difficult to treat and control.\(^{34}\) Two post-discharge patients died of drowning during generalized tonic-clonic seizure. Therefore, unconsciousness caused by generalized tonic-clonic seizure could indirectly increase mortality. In this study, the time needed for intelligence decline could not be ascertained because of the absence of repeated examinations of cognitive functions after hospital discharge. In addition, mild mental retardation is usually unnoticeable until school age.

**Public health implications.** By any standard, JE is a major public health problem that can potentially be controlled by proven effective vaccines. However, policymakers in most Asian countries do not consider immunization against JE a priority in their public health programs. Our study reveals a high frequency of JE disability and discloses a far greater burden of long-term disability caused by JE than has been appreciated previously. Our results thereby support the case for introducing JE vaccine into countries in which JE is endemic but without a JE immunization program.

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