CLINICAL SEQUELAE AFTER JAPANESE ENCEPHALITIS: A ONE YEAR FOLLOW-UP STUDY IN THAILAND

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INTRODUCTION

The neurological signs and symptoms of Japanese encephalitis (JE) during the first 60 days of illness have been well described in the medical literature (Sabin, 1947; Hullinghorst *et al.*, 1951; Dickerson *et al.*, 1952; Lincoln and Sivertson, 1952; Ketel and Ognibene, 1971), and several studies describe sequelae present for one or more years after disease onset (Simpson and Meiklejohn, 1947; Goto, 1957; Pieper and Kurland, 1958; Richter and Shimojyo, 1961; Grossberg *et al.*, 1962). No report, however, has quantified neurological deficits in a way which allows prognostication of recovery after one year of convalescene. This is important in order to assist the physician in dealing with the patient and with the patient's family. Estimates of the probability that a given neurological sign will remain abnormal can also be used to suggest specific remedial therapy.

This is a report of a prospective study designed to measure intellectual, behavioral and motor performance, and EEG results in Thai patients studied acutely during, and one year after the 1970 JE epidemic in Northern Thailand. Neurological deficits were measured in a manner which allows prognostication of recovery of several important neurological sequelae. In addition, the effects of age and sex on severity of the acute illness and on the degree of clinical recovery were examined. The present study provides a basis for another report which examines the interaction of prior group B infection and clinical sequelae (Edelman *et al.*, in preparation).

† The opinions and assertions in this paper are the private views of the authors and do not necessarily reflect official views of the United States Department of Defence.

MATERIALS AND METHODS

Subjects: One hundred and ninety-five individuals (122 males and 73 females) were initially considered for inclusion. They were residents of the Lampang and Chiang Mai Valleys in Northern Thailand, who were admitted to one of five area hospitals during the 1970 JE epidemic, with signs and symptoms of febrile encephalitis. Of the 195 individuals, 15 were eliminated because they lived too far away for follow-up, two refused to cooperate, and seven were subsequently diagnosed as having other diseases. Thirty potential subjects were eliminated on the basis of negative JE serology. Thirty-five individuals with fever and encephalitis died. A serologic confirmation of the JE diagnosis is available on only six (6) of these thirty-five (35) patients. Data for this report were gathered concerning the 35 patients who died and from the 106 surviving patients whose diagnosis was serologically confirmed. The age range of these 141 (35 dead+106 surviving) subjects was from 1 to 47 years. There were 68 males and 38 females among surviving patients and 21 males and 14 females among patients who died. Criteria for inclusion are presented in Table 1.

Study Design

Subjects were examined during the acute stage (first 30 days after disease onset) and

Table 1

Clinical and serological criteria used for inclusion into study.

All patients (confirmed and presumed JE)

1. Fever: Recent positive history or oral temperature > 38° C.
2. Neurological: Central nervous system signs and symptoms present by recent history or physical examination (minimum symptoms of headache and stiff neck required).
3. Cerebro spinal fluid : When obtained, sterile on bacterial culture and cell count compatible with aseptic meningitis (10-1000 cells per cmm).

JE Confirmed

Whole serum HI or CF antibody titer rise (≥ 4-fold) to JEV alone and/or serum IgM monospecific HI antibody titer rise to JEV (Edelman and Pariyanon, 1973).

JE Presumed

Whole serum HI or CF antibody titer rise (≥ 4-fold) to JEV and to one or more dengue virus serotypes.

or

Fixed, elevated (≥ 1 : 80) or falling (≥4-fold) serum HI or CF antibody titer to JEV alone.

or

Serum JEV monospecific IgM HI antibody fixed, falling or present in an unpaired serum.

or

Patient died with acute aseptic meningo-encephalitis but low fixed serum HI and CF antibody titer (≤1 : 40) in unpaired serum or in paired sera drawn less than 7 days apart.

during convalescence, between 370 and 420 days after onset (median equals day 390). A physical and neurological examination was performed on hospital admission; standard forms were utilized to record results. Blood was drawn and cerebrospinal fluid (CSF) was collected by lumbar puncture in 78% of patients. About 80% of patients underwent neurological examination twice during the acute stage. In these patients a sign was recorded as abnormal if either examination detected an abnormality. Electroencephalographic (EEG) examinations were also conducted. An intelligence test (the "Memory Test") was administered to patients who had recovered enough to respond. Public health nurses visited homes, schools, and places of employment to gather additional information. These nurses interviewed family members and teachers or employers, and examined the patient in these environments. Information collected from these sources dealt principally with social adjustment, but included observations of neurological symptoms. EEG examination, intelligence testing, and the visit to the patient's home were not scheduled until he was ready to be released from the hospital. Identical examinations were performed during convalescence.

One of a panel of five physicians performed all acute and either one of two physicians performed all convalescent neurological examinations. All examinations were conducted in the Thai language. Hospital records were occasionally reviewed to obtain missing data. The Memory Test was developed in Thailand to measure short-term memory (Xumsai, 1962). It requires that the location of "X" marks on various complicated geometric

designs be recalled immediately after a subject examined each design.

Except for the EEG and psychometric test, all data reported here were recorded by at least two different observers. No attempt was made to assess inter-rater reliability. The psychometric test was administered to individuals above age seven. Comparisons presented in this paper are based on nine clinical variables derived from information collected as described above. The clinical variables are:

1. Level of Consciousness: Recorded as normal if the patient was alert or dull, and abnormal if the patient was in semicoma or coma.

2. Convulsions: Scored as normal (absent) or abnormal (present).

3. Motor Paralysis: Scored as normal or abnormal. Any paralysis, weakness, gait abnormality, or foot drop was scored as abnormal, but the degree of deficit was not graded.

4. Tremor: Scored as normal (absent) or abnormal (present). Any tremor or involuntary movement was scored as abnormal, but intensity was not graded.

5. Ataxia: Scored as normal (absent) or abnormal (present). Intensity of ataxia was not graded.

6. Muscle Tone: Scored as normal or abnormal. Any rigidity, spasticity, or flaccidity was considered abnormal.

7. EEG: Scored as normal or abnormal. All judgments were made by one neurologist specially trained to interpret the EEG. Generalized, focal, and multi-focal tracings were classified abnormal.

8. Emotional Behavior: Evaluated on a scale comprised of the following 14 signs and symptoms: irritability, inability to perform everyday tasks independently, headaches, "unusual" behavior, echolalia, rejection by friends, aggressiveness, hallucinations or delusions, restlessness, irritation to others, paranoia, sleep disturbance, incontinence, and depression. Each item was judged either as abnormal or as normal (i.e., not different from expected behavior or behavior prior to onset of JE). The percents of these items abnormal for subjects in given groups were calculated for tabular presentation.

9. Memory Test: Scores were rated as retarded (two or more standard deviations (S.D.) below the mean of the patient's age group); dull (from one two S.D. below the mean), or normal (all others). Ratings were based on norms (Xumsai, 1962) derived from Thai people living in rural areas south of Bangkok, Thailand. This test was only applicable to persons above seven years of age.

RESULTS

JE terminated fatally in 25% of all cases (Table 2). Mortality was greater for younger than for older patients. The median number of days from disease onset to death was fewer for the younger than for the older patients.

CSF white cell counts and protein concentrations were not significantly different for younger and older patients (Table 3). The mean CSF cell counts and protein concentrations for those patients who survived and for those who later died, irrespective of their age, were not statistically different by independent *t* test.

Table 4 presents the per cent of subjects with abnormal signs during the acute and convalescent stages. During the acute stage younger subjects had significantly greater abnormalities than older subjects for the symptoms of convulsions, motor paralysis and EEG. Except for the Memory Test, on which older patients showed greater abnormalities (larger per cent mentally retarded, smaller per cent normal), there was little diffe-

Table 2

Percentage of deaths by age groups.

Age group	Status		% Death	Median No. of days after onset to death
Younger	Surviving	(n = 54)	-	-
(10 years or less)	Died	(n = 23)	30%	3.7
Older	Surviving	(n = 52)	-	-
(11 years or more)	Died	(n = 12)	19%	7.5
Total	Sviinrvu	(n = 106)	-	-
	Died	(n = 35)	25%	5.5

Table 3

Results of CSF examination.

Age group	Status	Mean cell count per c.mm ± S.D.	Mean protein concentration mg% ± 1 S.D.
Younger	Surviving	147 ± 134 (n = 52)	80 ± 59 (n = 30)
	Died	207 ± 135 (n = 15)	106 ± 76 (n = 11)
	Combined	160 ± 136 (n = 67)	87 ± 64 (n = 41)
Older	Surviving	224 ± 252 (n = 42)	89 ± 67 (n = 34)
	Died	223 ± 227 (n = 4)	149 ± 185 (n = 5)
	Combined	224 ± 251 (n = 46)	97 ± 89 (n = 39)
Total	Surviving	181 ± 201 (n = 94)	86 ± 64 (n = 64)
	Died	210 ± 151 (n = 19)	120 ± 116 (n = 16)

rence between age groups on other signs scored during the acute stage.

After one year of convalescence, subjects improved on all neurological signs, but younger subjects showed significantly greater abnormalities than older subjects for motor paralysis, ataxia, muscle tone, and EEG. In contrast to these findings of greater neurological abnormalities in younger subjects, the Memory Test scores of older subjects, at the end of one year of convalescence, were more abnormal.

Data listed in Table 5 provide some indication of the overall severity of the disease. There is a trend for younger subjects to have more neurological symptoms during both the acute and convalescent stages. Seventy-nine per cent (79%) of younger subjects and 72% of older subjects had more than one neurological abnormality during the acute stage. After one year of convalescence, 27% of younger subjects and 6% of older subjects had more than one abnormality.

Table 6 lists the neurological condition at convalescence based on subjects' condition during the acute stage. These data indicate that individuals graded "abnormal" rather

Table 4

Evaluation of signs during first 30 days and after one year.

Sign	Age group		Acute stage		Convalescent stage	
			No. patients	Per cent abnormal	No. patients	Per cent abnormal
Level of consciousness	Younger		53	71	54	0
	Older		52	64	52	0
Convulsions	Younger		54	83**	51	8
	Older		52	50	48	4
Motor paralysis	Younger		48	41**	52	25**
	Older		48	17	49	6
Tremor	Younger		49	55	52	19
	Older		46	54	48	18
Ataxia	Younger		39	36	47	16*
	Older		44	39	48	4
Muscle tone	Younger		52	60	51	17*
	Older		48	59	48	4
EEG	Younger		38	82*	50	64**
	Older		31	55	47	30
Emotional behavior	Younger		54	64	52	29
	Older		52	59	50	25
Memory Test[a]	Younger	Retarded	3	23	0	0
		Dull	7	64	1	8
		Normal	3	23	12	92
	Older	Retarded	22	61	4	11
		Dull	10	28	11	30
		Normal	4	11	21	59

* Difference between younger and older significant at $p<.05$, chi square test.
** Difference between younger and older significant at $p<.01$, chi square test.
[a] Differences not tested statistically due to small sample sizes in younger groups.

than "normal" during the acute stage for any sign are more likely to be "abnormal" for that sign after one year of convalescence. More improvement occured for some signs, such as convulsions and ataxia, than for others, such as motor paralysis and muscle tone.

A comparison of disease severity for males and females indicated no reliable differences; differences favoring either sex were not consistent, and the magnitude of difference was not remarkable for any sign.

Table 5

Percent of patients having various numbers of abnormal neurological symptoms during acute and convalescent periods.

Total number of abnormal signs per patient	Per cent of Patients[a]			
	Acute stage		Convalescent stage	
	Younger	Older	Younger	Older
0	4	8	63	73
1	19	24	10	20
2	19	30	12	4
3	32	24	8	-
4	21	14	8	2
5	6	-	0	-

[a] During convalescence we were unable to obtain complete information on two younger and three older patients. These are excluded from this table.

DISCUSSION

Antemortem observations made on 35 patients who died were deleted from analysis since one purpose of this study was to permit prognosis of recovery of normal neurological function one year after acute illness. All 35 deaths occurred before one year had elapsed; 29 subjects died during the first 30 days of illness. Only six of the deceased patients had been confirmed serologically as having JE, but all had neurological signs and symptoms of febrile encephalitis during the JE epidemic. Thus, all 35 are presumed to have died of JE infection. This assumption is supported by

Table 6

Neurological condition at convalescence as a function of acute condition.

Sign	Age	Acute condition N = Normal ABN = Abnormal[a]		Convalescence. Per cent Normal	Per cent Abnormal
Convulsion	Younger	N	(9)	100	0
		ABN	(49)	84	8
	Older	N	(27)	88	0
		ABN	(27)	88	6
Motor paralysis	Younger	N	(29)	79	10
		ABN	(23)	62	26
	Older	N	(39)	92	0
		ABN	(10)	70	20
Involuntary movement	Younger	N	(23)	80	8
		ABN	(29)	72	17
	Older	N	(22)	84	9
		ABN	(25)	72	24
Ataxia	Younger	N	(26)	88	4
		ABN	(14)	79	14
	Older	N	(28)	93	0
		ABN	(17)	82	7
Muscle tone	Younger	N	(23)	85	8
		ABN	(32)	55	28
	Older	N	(20)	90	0
		ABN	(29)	86	7

[a] Six patients who survived the acute stage (first 30 days) died before 1 year. These patients were not scored as normal or abnormal but instead as "missing data". Thus the total per cent in some convalescent categories does not equal 100. Numbers in parentheses are frequency of each type of patient (Normal or Abnomal).

data (Grossman *et al.*, 1973) indicating that no infectious encephalitic agents other than JE virus could be detected during this epidemic. The poor physical condition of a few patients during the acute stage of illness precluded meaningful evaluation of all neurological signs. This accounts for some missing data during this period. We were also unable to obtain a hospital neurological examination at convalescence on two younger, and four older, patients; however, some of this information was collected during home visits by nurses. Despite these limitations, we were able to reach certain conclusions that may prove useful to the clinician managing patients with JE.

The case-fatality ratio in our patients (25%) was close to that reported by Goto (1957, 1962) in Japanese patients in 1948, but considerably higher than that reported by investigators studying JE in American troops in Japan, Vietnam and Korea. The case-fatality ratio in American troops ranged from 2-10% (Sabin, 1947; Dickerson *et al.*, 1952; Lincoln and Sivertson, 1952; Grossberg *et al.*, 1962; Ketel and Ognibene, 1971). The lower ratio in Americans compared to Asians may be due in part to speed of hospitalization, older age of patients, greater availability of supportive nursing care, and generally good health of the American patients.

The sex ratio of almost 2:1 (male to female) for hospitalized patients suggested possible sex-related susceptibility to JE. If males were more susceptible, they might be expected to have had more severe neurological deficits during the acute and convalescent stages. Examination of the data, however, shows no consistent difference of neurological abnormalities between sexes during either time period. Pieper and Kurland (1958) also report no sex-related differences in disease severity. The higher incidence of clinical illness for males could result from sex-related behavior; perhaps males are more likely to work outside late in the evening when they would be exposed to JE virus-infected vector mosquitoes (Grossman *et al.*, 1973).

The case-fatality ratio in younger subjects was 50% higher than in older subjects, and the average number of days to death was about half of that for older patients (Table 2). The observation that younger patients were hospitalized more quickly than older ones (2.3 days *vs* 3.4) mitigates the validity of delay of treatment as the explanation. Rather, younger patients may have had more severe JE virus infections which resulted in higher mortality and a shorter clinical course before death. If true, this interpretation should be supported by observations of more clinical sequelae in younger survivors than in older survivors, providing that death did not select out all of the more severely ill patients. The data in Table 4 indeed indicate that during the acute stage, three of seven neurological complexes were significantly more abnormal in younger patients, while both age groups showed similar percentages of abnormality for the remaining four signs.

During convalescence, recovery was reflected by improvement in each of the seven neurological signs. However, for four of these signs younger subjects exhibited significantly more abnormal function than older patients. The large percentage of abnormal EEG responses recorded after one year is striking, especially for younger patients, in whom 50% of EEG's were interpreted as abnormal. This might indicate a propensity toward abnormal EEG in the young, residual brain damage not reflected in the other complexes measured, or brain damage which has been clinically compensated.

Abnormal "emotional behavior" might be a clinical manifestation of the neuropathologic changes causing abnormal EEG tracings. The significance of abnormal scores on the emotional behavioral symptom complex is

difficult to interpret as expected scores based on a "healthy" Thai population are not available. However, the items making up this symptom complex were selected to measure variables which probably relate directly to the individual's abilities to integrate into society and to cope. Abnormality on many of these items often indicates a need for psychiatric follow-up.

The only sign on which younger patients present as consistently less impaired is the Memory Test, which is designed to measure intelligence. It is clear that intellectual functioning was severely affected for both age groups during the acute stage, and for older rather than younger subjects at convalescence; however, this may be an artifact due to the small number (thirteen) of younger patients tested. Scores on this test indicate that many subjects were functioning below normal ranges. But these patients certainly were less impaired than those evaluated by Goto (1957), who reported 50% of his subjects to be mentally retarded (at least two standard deviations below the mean) five years after disease onset.

From the data in Table 5, it appears that older patients have fewer multiple abnormalities during the acute and convalescent stages of illness. Moreover, a slightly larger percentage of older patients was scored normal in all symptom categories at convalescence. The important variable of "degree of impairment" of any one symptom was not ascertained in this study. Japanese investigators first suggested the existence of age-related sequelae, reporting the same incidence of JE in persons age 15 and under and those 16 and older, but more severe sequelae in the younger patients (Goto, 1957). Pieper and Kurland (1958) reported higher incidence of sequelae in Guamanian patients 0 to 9 years of age than in older persons. This trend towards age-related differences might reflect greater immunity in older patients due to prior group B arbovirus infection (Edelman *et al.*, in preparation; Grossman *et al.*, 1973), or reduced virulence of the JE virus in older patients.

Results in Tables 4 and 6 can be used by Southeast Asian physicians to estimate the probability that a JE patient will have neurological abnormalities at one year based on his neurological condition 30 days after disease onset. All individuals who survived the acute stage are included in Table 6, including the six patients who later died. Thus, if a patient survives beyond the first 30 days, chances of death are about 5% (6 out of 112). For those who survive the acute stage, but who have some neurological abnormality, the chances of complete recovery are generally not higher than about 80%. This information might direct physical therapy and patient and family follow-up in an attempt to effect greater recovery. Goto (1957) reported that 75%, and Simpson and Meiklejohn (1947) reported that about 30% of their Japanese patients had some abnormal sequelae one year after onset. Goto (1957, 1962) indicated that continued over-all improvement can be expected for the first three to five years after disease onset. The mean values of CSF cell counts and protein concentrations were not different in the two age groups, nor were they different in those patients who survived and those who died (Table 3). These results confirm previous reports indicating that CSF protein and cell count cannot be used to guide prognosis (Dickerson *et al.*, 1952; Lincoln and Sivertson 1952).

SUMMARY

One hundred and forty one (141) Thai people were studied acutely and at one year after onset of Japanese encephalitis. Thirty-five individuals died and more than 30% of survivors had some neurological abnormality after one year. Memory loss and abnormal EEG were common sequelae. Sex had no

bearing on severity of the disease but younger people (age 10 or younger) appeared to be at higher risk than older people (age 11 or older) for fatal termination and for sequelae. Data are presented in a manner which allows the physician in Southeast Asia to estimate the probability that a given symptom will remain abnormal after one year of convalescence.

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