

A Follow-up Study of Japanese Encephalitis in Northern Thailand

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Examination of the medical literature indicates that there are many studies of Japanese encephalitis describing the critical symptoms present in the first 60 days after disease onset. There are, however, few studies which present data on convalescence beyond this acute stage. These latter studies present information collected from 1-15 years after onset of Japanese encephalitis (JE).

The only detailed long term study of JE was done by Goto, who eventually followed 43 cases for 15 years. His work is, however, of limited utility to other physicians. This is because most of his reports have been only in Japanese, and since one cannot derive from his work what definitions were utilized for memory loss, mental impairment, disease severity, etc., the physician cannot utilize this information to aid in decision making and counselling processes.

None of these studies has adequately examined one of the most important effects of JE, that of intellectual impairment. Information in this area has usually been limited to a general statement indicating lower intellectual performance; none has quantified data either during the acute phase or during convalescence.

In addition, no study (with the exception of that by Goto) which has continued beyond the acute stage has presented evidence for anything but very gross neuropathology, intellectual deficit, or mental status abnormalities.

The importance of age as a determinant of severity of onset and degree of recovery has generally not been considered. Age is important because younger individuals appear to be at higher risk for sequelae than older people. Thus, one is more likely to find severe sequelae in patients below about age 10 to 15.

We feel that one of the most important contributions of research in this area is to provide the physician with information which will help him determine the probable outcome or prognosis of this disease. This would allow him increased efficiency in deciding who, for example, should receive occupational therapy, physical therapy, more intensive follow-up, etc., in order to ensure most complete recovery; and to provide information for the most accurate counselling for family and friends of the patient. Thus, the physician could more adequately describe the probability of a given symptom being present, for example, one year after onset of the disease.

The following studies have responded to these points. Dickerson, et al, did a complete study of U.S. soldiers who contracted JE in 1952 in Korea. He attends to the problem of prognostication and indicates that a long fever or presence of a positive Babinski sign indicated a serious outcome. These symptoms predicted either death or neurological residuals at 10 weeks. No further follow-up was obtained. Goto indicates that individuals who acutely present with hyperkinesia have a more favorable prognosis than those presenting with hypokinesia. Pieper and Kurland report that acute convulsions and neuronal involvement correlate with sequelae ten years later. No specific figures are given.

The present study was designed to more adequately measure intellectual performance and provide greater detail on some of the possible correlates of the severity in JE. Thus, we will closely consider possible age differences, sex differences, and quantification of intellectual impairment. These will be presented in a manner consistent with maximal prognostic value.

METHOD:

Subjects: One hundred and ninety-six individuals (125 male and 71 female) were initially included. Population characteristics (stability, education level, occupation, etc.) are described in the previous annual report. All were residents of the Chiang Mai Valley in northern Thailand who presented to one of the local hospitals with symptoms indicative of possible JE infection. Only those 119 individuals (77 male, 42 female, average age 11.1, S.D. = 7.7), whose diagnosis could be definitely established serologically as Japanese encephalitis and who agreed to cooperate, were retained for study. Eleven of the 196 subjects were eliminated as they lived too far away for follow-up, 3 additional patients refused to cooperate, and 8 were definitely diagnosed as non-JE. Fifty-five subjects were eliminated because they were serologically negative for JE, or because they died ($n=37$) and no serological diagnosis could be made.

Apparatus: Standard forms were constructed to record state of convalescence. These forms were: a) Mental Status—to measure psychiatric aspects of subjects' convalescence; b) Neurological—to measure present neuropathology; c) Physical Examination—to describe physical condition as well as certain neurological conditions; d) Home and School—to record feedback from the family, teacher, or employer on a variety of neuropsychiatric symptoms, and provide direct observation of the subject in these environments; e) EEG—to record electroencephalogram findings.

In addition, hospital records were scrutinized to obtain additional or missing data. Objective psychometric tests were also utilized. Those selected were: a) Three Sub-tests from the WAIS or WISC (digit span, digit symbol, and block design) and b) the Memory Test (to measure short-term memory). This latter test was developed in Thailand and requires the subject to recall the location of "X" marks on various complicated geometrical designs.

Procedure: Each patient went through an identical sequence of examinations. All record keeping was done on the forms described above. Any patient who reported to the out-patient clinic of one of the five participating hospitals between 10 May and 30 October 1970, and whose clinical picture resembled that of JE was included in the study. These patients were referred to one of the six participating physicians for a physical examination, blood drawing, and in some cases drawing cerebrospinal fluid (CSF). As soon as the patient's health allowed, he was transported to the one hospital where neurological, mental status, and psychometric examinations were conducted. One of two physicians conducted all neurological examinations, one psychiatrist conducted all mental status examinations, and one of four psychologists conducted psychometric examinations (only patients above seven years of age were so tested). EEG examinations were also conducted. Those patients in which JE could not be confirmed were excluded from the data analysis.

At discharge patients were given appointments to return to the hospital. These return visits were scheduled at 1, 2, 4, 6, 9 and 12 months following discharge. Each visit required one full day of examination. This schedule was followed as closely as practicable. On each return visit blood was drawn and the patient received the same examinations described above.

On the same follow-up schedule, one of two SMRL public health nurses visited patients' homes and schools or places of work. On each of these visits the Home and School form was completed. This was based on information asked of family members, teachers or employers, and from personal examination of the patient. Questions dealt primarily with social adjustment but included observation of neuropathological signs and symptoms.

RESULTS: All comparisons presented in this paper are based on the following eleven clinical variables; these were evaluated each time a subject was examined.

1) Level of Consciousness: recorded as normal as long as the patient was alert or dull. 2) Emotional Behavior: this is a 15-item scale made up of items such as irritability, aggressiveness, restlessness, paranoia, incontinence, and depression. For each item scored as "normal" the subject received a score of 1. Total normal items for each subject were presented as a per cent of the total symptoms on which information was available to score on that subject. Thus, a score of 50% indicates that the subject was normal on 50% of those items on which information was available; the total number of items scored was not always 15. 3) Memory and Intellect: this is a 6-item scale based primarily on how supervisors rated work and school performance. 4) Convulsions: these were scored as either present or absent. 5) Motor Paralysis: this was scored normal or abnormal. Any paralysis, weakness, loss of muscle strength, gait abnormality, etc., was considered abnormal. 6) Involuntary Movements or Tremor: subjects were scored as normal or abnormal. Abnormal was considered to be the presence of any involuntary movement or tremor. 7) Ataxia: subjects were scored as normal or abnormal. Any ataxia was considered to be abnormal. 8) Tone; subjects were scored as normal or abnormal. Any rigidity, spasticity, or flaccidity was considered abnormal. 9) EEG: subjects were scored as normal or abnormal. 10) Digit Span, Digit Symbol, and Block Design: scores on each were converted to a percentile score based on American norms from the WAIS or WISC. 11) Memory Test: scores were recorded as normal or abnormal based on Thai norms.

Observations from the seven follow-ups are presented for four time zones. The first zone consisted of the first 30 days after disease onset, the next two time zones consisted of 100 days each and the last time zone consisted of all convalescence after 230 days. Any symptom which was abnormal at any time in a time zone was recorded as abnormal. Some subjects may have had two or three observations made during a time zone. For psychometric testing the average score was selected if more than one observation was made. Few subjects were completely omitted for an entire time zone. Most symptom scores were recorded during each follow-up by more than one observer. If either reported abnormality for a symptom, "abnormal" was scored.

The results based on nine clinical variables are presented for younger (age 0-10) and older (age 11 and older) subjects for each of the four time zones in Table 1. Average days before hospitalization for younger patients was 3.3, and for older patients it was 4.0.

Examination of Table 1 indicates that on almost every symptom there is improvement for each age group between time zone I and time zone IV. In addition, we see a consistent pattern of greater improvement for older subjects and a higher level of functioning during the acute phase. The only exceptions to this are for ataxia; younger subjects apparently had less ataxia during the acute phase. On memory and intellect there was an apparent decrement in performance for both groups following the first time zone.

Psychometric test scores are presented in Table 2. It is apparent again that there is a consistent trend towards improvement from the first through fourth time zone. It should be noted that scores for the first three tests are based on American norms and are percentile rankings. The average percentile ranking should be 50 for a normal population. The 4th test is based on Thai norms and the average per cent normal for all subjects in each time zone is presented. The first three tests indicate that by Zone IV, subjects were responding relatively close to expected American norms (50%), but on the Memory Test only 44% fell within the normal range based on Thai norms.

Table 3 presents the percentage of subjects who were normal and abnormal in Zone IV as a function of their status in Zone I. Reference to this table indicates that those subjects who were normal during Zone I were more likely to be normal during Zone IV than subjects abnormal during Zone I.

Table 4 presents the percentage of individuals having various numbers of abnormal symptoms during Zone I and IV. Inspection of this table indicates that no individual was completely normal during Zone I; and about 23% of individuals, both younger and older, were completely normal at Zone IV. Older subjects again appear to have fewer abnormal symptoms, both at Zone I and Zone IV.

Table 5 presents results of CSF examination. Inspection of this table indicates that there are no differences between younger and older or living and dying subjects on cell count or protein mg%. As all differences were well within one standard error of each other no formal statistical tests were conducted.

DISCUSSION: The analysis scheme utilized was selected to allow the most efficient presentation of large amounts of data. In a longitudinal study such as this, it is inevitable that some observations will be omitted. To help compensate for this, the period of convalescence was divided into the four time zones described earlier. This usually provided two follow-up visits per time zone, and greatly reduced the number of subjects on whom no observations were made for an entire time zone. It should be noted that observations could have occurred at any time during a given zone. The use of "per cent normal" for the multiple item "symptoms" (emotional behavior, and memory and intellect) also helped eliminate missing data due to inapplicability of this for preschool populations. The symptoms were scored only on the basis of the home visit for these younger patients.

The symptoms presented (with the exception of EEG and psychometric testing) were all recorded by at least two observers during the hospital or home visits. If any observer recorded an abnormality, the symptom in question was recorded abnormal. This is to ensure that no abnormality was omitted. No attempt was made to assess inter-rater reliability.

The Japanese investigators first suggested age effects, reporting the same incidence of infection in younger and older subjects (older were 16 years of age), but more severe sequelae in the younger patients. Hullingshorst, et al, found that 63% of his Korean patients were 2 to 12 years old. Pieper and Kurland report relatively higher incidence of sequelae in children age 0-9 than in older subjects. Present results indicate that the older patient will have, on the average, a less severe onset and is likely to have a more complete recovery. These results are presented in Table 1. Level of consciousness was analyzed as an acute symptom only; no subject-evidenced disturbance in this area lasted longer than 30 days.

The symptom which samples the greatest variety of behavior is "emotional behavior." The items selected for inclusion in this scale were chosen from several of our forms and cover mental status and social adjustment. We see that even after 230 days individuals are, on the average, normal on less than 75% of the areas included in this symptom complex.

The "memory and intellect" symptom complex was made up of six items which consisted mostly of work and school performance. Again, we see that by the fourth time period individuals average less than 75% normal for the areas measured. The large Zone I values here are probably an artifact, as those patients who were too sick to go to school or work during Zone I were not measured. The remaining subjects (the most healthy) remained. By Zone II, when the most severely ill patients could be included for measurement, the averages for the groups become much lower.

It is apparent that most of the symptoms indicating neuronal damage do not show a great amount of abnormality. One striking finding was the large percentage of abnormal EEG responses recorded even after 230 days. This is especially true for the younger patients, for whom only 35% normal EEG's were reported. This might indicate a great deal of residual brain damage which is not directly related to the other symptoms measured, or brain damage which has been compensated.

Scores on the psychometric tests (See Table 2) generally do reflect a decrement in memory and visual—motor performance. American norms were utilized to score the digit span, digit symbol and block design. From these norms we calculated a percentile ranking. We see that on the digit span this value has been exceeded but on the digit symbol and block design it has not quite been reached. On both the digit symbol and block design scores appear to be still rising. These tests should all be sensitive to memory loss, and the latter two (digit symbol and block design) sensitive to difficulties with visual—motor coordination. On the basis of these tests, we conclude that average memory loss is not great. It is possible that these scores are all biased in an unknown direction due to the utilization of American norms; no Thai norms exist.

Thai norms for each age have been established for the Memory Test. We see that by Zone III Memory Test scores have levelled off at only about 44% normal. Thus, 56% are below normal. This is a quite different result from the other three tests, and is perhaps more consistent with the findings presented in Tables 1 and 2. We conclude that memory loss is a reliable effect of JE. This has been consistently reported in the literature, but has never been quantitatively measured.

It is apparent that a consistent pattern of greater disease severity for younger patients has emerged. This cannot be ascribed to time of hospitalization (younger patients were hospitalized earlier, which is consistent with a more severe disease onset) or differences in supportive care (18 younger patients and only 5 older patients received physical therapy). One might speculate that these differences might reflect different virulence of the infecting agent, due to older individuals having developed partial immunity after prior exposure.

Table 3 allows determination of the probability that a particular symptom will be abnormal after approximately 3/4 of a year of convalescence. We can see that most people who have a symptom abnormal during Zone I recover by Zone IV. Relatively few cases exist in which a symptom was recorded as normal during Zone I but abnormal during Zone IV, and these few probably represent individuals who were too ill to be adequately evaluated during Zone I. For example, due to the generalized weakness that accompanies JE, motor paralysis might easily be overlooked until the patient's strength returned. This table can be utilized to help predict patients' later convalescent status, based on the acute (Zone I) level of functioning.

Table 4 provides a general impression of the overall severity of the disease. It is based on a count of symptoms in Table 1 which were abnormal (excluding emotional behavior and memory and intellect and including the Memory Test). Every subject had some abnormality during the first time zone: most subjects had between three and five symptoms abnormal. By the fourth time zone 23% of younger and older subjects are normal, and there has been a shift to having fewer abnormal symptoms for the remaining subjects. Again, it appears that older subjects have fewer numbers of abnormal symptoms than younger subjects. Goto reported that about 75% of his subjects still had sequelae after three years (both young and old). Simpson and Meiklejohn report about 30% of their patients had some neurological sequelae one year after infection; however, they were able to follow only 1/3 of their original sample. The degree of behavioral impairment that these sequelae portend cannot be determined from these data.

Table 5 presents cell count and protein mg% found in CSF. There is no difference in mean values for either measure between the two age groups. In addition, there is no difference between those patients who are living and those who later died. The deaths were those 35 individuals who died too early to establish serologically the presence of JE virus.

We have spent little time discussing those 35 patients who died. We presume they were JE and this would give a death rate of about 24%. This is consistent with the Japanese literature, but about double that reported by Dickerson, et al, based on American troops in Korea. More recently, Ketel and Ognibene reported only one death out of 57 infections among Americans in Vietnam. This difference can probably be ascribed to the level of supportive nursing care available during the acute illness.

In conclusion, it is apparent that while many deaths occurred, survivors recovered relatively well. Few had residuals after nine months which were severe enough to interfere with their behavioral adjustment. The present study should allow accurate prognostication of sequelae in future outbreaks of this disease in South East Asia. The consistent age differences cannot be adequately explained at this time.

Table 1.
Percent of Subjects Normal by Symptom for each Time Zone

Symptom	Age Group	Time Zone			
		I	II	III	IV
		0-30 days	31-130 days	131-230 days	231 days or longer
Level of Consciousness	Older	37%	—	—	—
	Younger	25	—	—	—
Emotional Behavior	Older	60	72%	74%	75%
	Younger	60	68	69	71
Memory and Intellect	Older	83	66	73	74
	Younger	81	63	68	62
Convulsions	Older	49	98	100	96
	Younger	13	94	100	92
Motor Paralysis	Older	78	92	96	94
	Younger	56	75	79	75
Tremor	Older	45	45	70	80
	Younger	41	58	74	80
Ataxia	Older	59	76	93	96
	Younger	67	81	79	84
Tone	Older	41	80	98	96
	Younger	39	69	82	78
E.E.G.	Older	42	47	65	71
	Younger	18	7	21	35

Table 2.
Psychometric Test Scores for each Time Zone¹

Psychometric Test	Time Zone			
	I 0-30 days	II 31-130 days	III 131-230 days	IV 231 or longer
Digit Span ²	30	42	46	57
Digit Symbol ²	7	22	24	33
Block Design ²	14	19	27	45
Memory Test ³	3	22	44	43

¹ Includes those 45 subjects age eight and older.

² Percentile ranking using U.S. norms.

³ Percent normal using Thai norms.

Table 3.
Percent Subjects Normal and Abnormal for each Symptom in Time Zone I & IV¹

Symptoms	Age	Zone I	Zone IV	
			N%	ABN%
Convulsion	Younger	N (9)	100.0	0
	Older	ABN (55)	69.1	7.3
		N (28)	82.1	0
		ABN (27)	85.2	7.4
Involuntary Movement	Younger	N (24)	75	8.3
	Older	ABN (32)	65.6	18.8
		N (22)	81.8	9.1
		ABN (26)	69.2	23.1
Muscle Tone	Younger	N (25)	80	8
	Older	ABN (34)	52.9	26.5
		N (21)	85.7	0
		ABN (29)	86.2	6.9
Memory Test	Younger	N	—	—
	Older	ABN (8)	87.5	12.5
		N	—	—
		ABN (19)	26.3	68.4
Motor Paralysis	Younger	N (30)	76.7	10
	Older	ABN (26)	53.9	23.1
		N (41)	87.8	0
		ABN (9)	77.8	22.2
Ataxia	Younger	N (27)	85.2	3.7
	Older	ABN (14)	78.6	14.3
		N (28)	92.9	0
		ABN (18)	77.8	5.6
E.E.G.	Younger	N (8)	37.5	50
	Older	ABN (35)	37.1	48.6
		N (14)	85.7	7.1
		ABN (18)	66.7	22.2

¹ Percent values do not usually equal 100 as individuals on whom data were not available are not scored normal or abnormal. Numbers in parenthesis indicate number of subjects in each normal or abnormal group.

Table 4.
Percent of Individuals Having Various Numbers of Abnormal Symptoms
During the First and Last Time Zones

No. of Symptoms Abnormal	Zone I		Zone IV	
	Younger	Older	Younger	Older
0	0.0%	0.0%	22.0%	23.5%
1	5.6	7.8	33.3	41.2
2	7.4	17.7	20.4	19.6
3	20.4	29.4	5.6	9.8
4	35.2	17.7	5.6	—
5	20.4	17.7	7.4	2.0
6	5.6	3.9	—	—
7	5.6	3.9	—	—
No data	—	2.0	5.6	3.9

NOTE — Includes 54 younger and 51 older cases.
6 deaths are excluded, as are 12 additional on cases which convalescent follow-up was not possible.

Table 5.
CSF Results

Patient Type	Cell Count per cu. mm.	Protein mg%
≤ 10 years	161 ± 136 (n = 67)	88 ± 64 (n = 41)
≥ 11 years	224 ± 252 (n = 46)	97 ± 89 (n = 39)
living	181 ± 201 (n = 94)	86 ± 63 (n = 64)
dead	211 ± 152 (n = 19)	120 ± 116 (n = 16)