

A PRELIMINARY REPORT ON ENCEPHALITIC TYPE OF ILLNESSES IN SINGAPORE

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CASES of encephalitis and aseptic meningitis are very much more common in Singapore than in England. The term "aseptic meningitis" embraces a multitude of conditions in both countries, but in Singapore the prognosis of this syndrome, whatever its ætiology, is not as benign as in England. A significant number of cases in Singapore suffer from sequelæ in the form of emotional and neurological disturbances. This group of illnesses also carries a significant mortality and, in view of the number of cases occurring, an attempt has been made to study them from a clinical and epidemiological point of view.

The General Hospital, Singapore, very kindly gave us permission to see the notes of patients who had been admitted with encephalitis and aseptic meningitis, and these were studied in conjunction with the notes available from the British Military Hospital. Although the first patient to come under our personal care was in May, 1955, the study was taken back to the beginning of 1954. Any

Table 1. *Monthly incidence of encephalitis during the three-year period 1954-56*
(figures in parentheses indicate the number of deaths)

Status	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Military ...	4	3	9	7	8	8	7	7	10	8	8	9	88 (15)
Civilian ...	21	16	22	24	19	17	18	21	26	19	21	21	245 (77)
Totals ...	25	19	31	31	27	25	25	28	36	27	29	30	333 (92)

It can be seen that there is no seasonal variation and the military and civilian population have a constant infectivity rate. The slightly higher death rate among civilians is possibly due to the relatively high incidence in children in this group.

Note.—In Tables 1, 2 and 4, "civilian" refers to local population (*i.e.* Malays, Chinese, Indians, Tamils). No Europeans are included amongst the civilian figures as they were private patients and no attempt was made to trace their old notes.

* At the time at which this survey was carried out, Major Dowling was D.A.D.A.H., Singapore Base District, and Captain Webb was Junior Medical Specialist at B.M.H., Singapore.

Table 2. *Distribution of military and civilian cases according to age group*
(figures in parentheses indicate the number of deaths in each group)

Age Group	1954-56		
	Military	Civilian	Total
Birth ...	4 (3)	38 (6)	42 (9)
6 months ...	5 (3)	22 (4)	27 (7)
1 year ...	2	26 (9)	28 (9)
2 years ...	2 (1)	20 (9)	22 (10)
3 years ...	1	23 (10)	24 (10)
4 years ...	4	14 (5)	18 (5)
5 years ...	8 (2)	53 (23)	61 (25)
10 years ...	11 (2)	18 (3)	29 (5)
20 years ...	33 (2)	14 (3)	47 (5)
30 years ...	12 (1)	8 (2)	20 (3)
40 years or over	6 (1)	9 (3)	15 (4)
Totals (all ages)	88 (15)	245 (77)	333 (92)

Table 3. *Analysis of all cases 1954-56 according to race and age group*
("European" represents the expatriate military population, except for the Gurkhas, who are included amongst the Indians)

Age Group	Totals						Total (all races)
	Race						
	Chinese	Malay	Indian	European	Others	No record	
Birth ...	33	2	2	1	3	1	42
6 months ...	19	1	4	2	1	—	27
1 year ...	24	1	2	1	—	—	28
2 years ...	19	2	—	1	—	—	22
3 years ...	19	2	3	—	—	—	24
4 years ...	10	1	3	2	1	1	18
5 years ...	46	2	3	8	—	2	61
10 years ...	16	3	—	9	1	—	29
20 years ...	9	9	2	26	1	—	47
30 years ...	4	1	3	12	—	—	20
40 years or over ...	6	—	2	6	1	—	15
Totals (all ages) ...	205	24	24	68	8	4	333

case notes which suggested a lower motor neurone lesion of the trunk or limbs were provisionally labelled as polio-myelitis and have not been included in the study. The same has also applied to those which showed a persistently low cerebro-spinal fluid sugar, suggesting a septic process. Including those cases personally seen, 333 case histories were available for study by the end of 1956. Tables 2 to 4 show the distribution of these cases according to age, race, civil or military status and length of stay in the island before the onset of the disease. The monthly incidence during the three year period 1954 to 1956 is shown in Table 1 and the case fatality rate according to age group in Table 5.

Table 4. *Further analysis of military cases and length of stay in Singapore before the onset of the disease*

(figures in parentheses represent the numbers of deaths in each group)

Length of stay in Singapore before onset of disease (in years)					Local inhabitants	No record	Total
Less than 1	1+	2+	3+	4 or over			
40 (8)	20 (1)	4 (2)	1 (0)	—	16 (4)	7 (0)	88 (15)

Note.—The 16 local inhabitants quoted are either Malay troops or their dependants serving with the British forces in Singapore.

Table 5. *Case fatality according to age group in the whole series*

Age Group (years)	Cases	Deaths	Case Fatality %
Birth	69	16	23.2
1 year	92	34	37.0
5 years	61	25	41.0
10 years	29	5	17.3
20 years or over	82	12	14.6
Totals (all ages)	333	92	27.6

No attempt has been made to draw definite conclusions from these figures because of several factors. These include the difficulty in tracing and interpreting old records, and also the racial differences reflected in hospital statistics for the civilian population. The Malay, who is of the Muslim religion, is much less inclined than the Chinese to bring his relatives to hospital, which may account for the relatively small proportion of Malays in Table 3. However, the comparison of age distribution of cases in the local and the European population (Table 2) is of interest. Among the local population, encephalitis appears to occur chiefly in young children (see also Fig. 1). Amongst Europeans, however, who represent a recently arrived community, the disease is distributed evenly through all age groups. This suggests that it is endemic in Singapore, and that some form of immunity is built up at an early age among the local population. Reports from

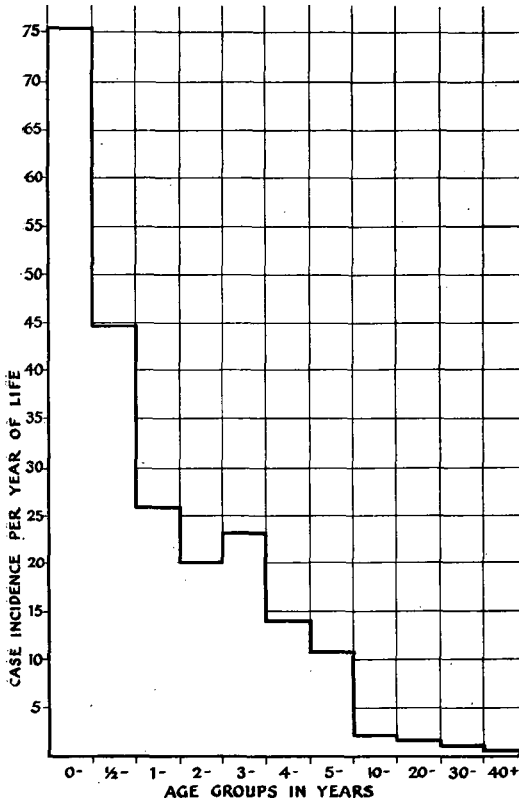


Fig. 1. Case incidence per year of life in each age group—civil cases only

Bangkok, Jakarta and Hong Kong indicate that they have a similarly high incidence of this type of illness. Whether the case distribution and aetiology is the same is not known at the present time.

CLINICAL PICTURE

This is characterised by severe headache, vomiting and fever for 24 to 48 hours before admission. The emphasis is on the headache which is described in phrases such as "It feels as if my head is going to burst." There is no relevant past history, but in a few cases other members of the family have had a severe headache and fever which have passed off without further incident. More careful questioning of the patient elicits in some cases that, although they have been at work until 24 hours before admission, they have not been completely fit because of a cough and generalised aches and pains.

Physical examination

The patients are generally febrile, but not necessarily so, with temperatures ranging up to 107° F. The impression gained is that the higher the temperature, the worse is the prognosis. The higher temperatures occur mostly in children.

Suffusion of the upper trunk and face is a fairly common feature, associated with conjunctival injection. They are mentally disturbed, the disturbances varying from gross hallucination to a mild but definite exaggeration of their own psychiatric type. In a few cases the original admission was to a psychiatric ward. Many are slow and unresponsive with a tendency to the Parkinsonian type of features. The latter may be due to the severe headache which is undoubtedly made worse by facial movements. There is usually discomfort on movement of the eyes, and in the severe cases conjugate movement of the eyes is lost.

Further examination at this stage commonly elicits no further abnormality. Important negative points are absence of lymphadenopathy, palpable spleen, rash and eschar. No abnormality is noted in the central nervous system apart from the mental change. Sometimes a stiff neck is present, but this is not an essential feature in the early stages of the disease.

Many cases never develop further than this stage. If, however, neurological complications do ensue they are frequently heralded by a convulsion. In such cases it is interesting to note that the fit is usually a focal one. Two patients are called to mind particularly, in whom myoclonic twitching commenced in the right hand, spread to the right side of the face, down the right arm and eventually down the right side of the body. From this preliminary stage of focal fits the disease often progresses to deepening coma and death. A few recover after a variable length of time, but the prospects of a full mental and physical recovery are poor after an illness as severe as this. The onset of coma is a bad prognostic sign in adults but not necessarily in children.

The neurological signs are pleomorphic. In the cranial nerves, abnormalities of the pupils and loss of conjugate movement of the eyes are those most frequently seen. Athetoid movements of the limbs occur and also many Parkinsonian features, such as cog-wheel rigidity and tremors. The tremors appear coarser than those usually seen in Parkinson's disease. Hemiplegias are common in the severer types of illness. The commonest lesion appears to be supra-nuclear and often associated with a hemiplegia and abnormal movements of the limbs. Other signs noted in some patients were a fall in the blood pressure, probably due to a central lesion causing peripheral circulatory collapse, and also minimal chest signs which were bronchitic rather than pneumonic. On no occasion have hæmorrhagic manifestations been noted in the skin or fundi. In children the history and findings on examination are similar, but fits are generalised rather than focal.

Disease of Gurkha infants

There is a syndrome which seems to fall into a category of its own, affecting particularly Gurkha infants. These infants are usually under 6 months of age and seldom over 18 months. Certain points in the history of their illness are very striking and show great similarity.

The child is usually well until a few hours before admission and, in many cases, a few hours before death. There is often the story of a mild respiratory tract infection during the previous week, but this has not been sufficient to

distress the child. On examination the child has a raised temperature, but its peripheries are cold, and there is a bluish tinge about the nails and lips. There is, in fact, a severe peripheral vaso-motor collapse. The respiratory rate may be slightly increased, but not usually to more than 40 per minute, and it is often irregular in type sometimes resembling Cheyne-Stokes respiration. The air entry over the lungs is good, and in many cases no adventitious sounds are heard on auscultation, but occasionally there are rhonchi and crepitations, particularly if the child has been in coma for some time. There are insufficient physical signs in the lungs to account for the cyanosed state, and the administration of oxygen does not materially help. If present, signs in the central nervous system appear to be confined to abnormalities of the pupils. Very soon after admission coma ensues, quickly followed by death. The whole course of the disease may last only twelve hours or less.

Because of the blueness, the slightly increased respiratory rate and the occasional signs in the chest, this syndrome has been attributed to an acute respiratory disease. However, the irregularity of respiration, the abnormality of the pupils and the profound peripheral vaso-motor collapse suggest a central origin for the condition.

These infants undoubtedly have a viral pneumonia as shown at post mortem, but in view of the cerebro-spinal fluid findings we feel that the principal cause of death may be a primary central nervous system lesion rather than a pneumonia.

Laboratory investigations

White blood count: This is commonly on the high side of normal, with a polymorphonuclear leucocytosis. Counts ranging from 7,000 to 24,000 cells per cubic millimetre have been observed.

Cerebro-spinal fluid: In several cases this has been normal on first tap in spite of well-established neurological signs. Within two to three days a pleocytosis has developed, usually lymphocytic, although in a few cases the initial count has been entirely polymorphonuclear. In the Gurkha infants, the chief abnormality appears to be in the protein, which is invariably raised but to a varied extent. Usually it is over 100 mg. per cent at the first tap with very few cells present (5 to 20), but high figures for protein (320, 420 and 615 mg. per cent) have been recorded. This tendency towards a high cerebro-spinal fluid protein is also occasionally seen in the adult, although sugar and chlorides are invariably normal.

Early tests suggesting a raised titre to the OXK antigen were not confirmed when using antigens from another source and results were ascribed to non-specific reactions with the hypersensitive antigen first used.

Post-mortem findings

Complete histological reports have not yet been obtained as the study of neuro-pathology is a very specialised one. However, in the fatal cases the histological reports available show that there was a definite encephalitic process taking place in the brain substance. Changes in the lungs have been variable and it is possible that there are at least two different types of central nervous system

disease, one without associated lung involvement and the other, chiefly in Gurkha infants, where the lung shows a pneumonic process in which the infiltrating cell is mononuclear and not polymorphonuclear. A point of importance arises here from the study of case documents of these children in the past. In many fatal cases the skull has not been opened because the cause of death has been assumed to be pneumonia. Also, for the same reason, many infants did not have a lumbar puncture, and it is suggested that all cases admitted to hospitals in FARELF with a history and findings as described above should have this investigation as a routine.

Sequelæ

Change in personality has been a common feature. Inability to concentrate, lack of confidence in doing things which are normally enjoyed and skilfully done, poor temper control and the inability to accept responsibility are the most frequent disturbances encountered. Reversal of sleep rhythm has been seen on several occasions. In one case the patient was admitted to the psychiatric ward with a provisional diagnosis of acute schizophrenia.

Organic neurological complications also occur in the form of Parkinsonism and hemiplegia. The latter is seen particularly in children who also tend to develop mental deficiency with a continued liability to fits.

TREATMENT

In the early stages of the investigation, circumstantial evidence indicated the possibility that the causative organism was of rickettsial type. For this reason, and in the absence of any known specific treatment for the disease, a trial was made of chloromycetin in the same dosage as for scrub typhus. Owing to the small number of cases treated, no significant assessment could be made of the effect of treatment. However, although it now seems unlikely that a rickettsial organism is involved, the impression was that chloromycetin was of benefit in some of the severe cases. Before any more definite statement can be given, a planned trial of treatment should be carried out.

In the management of the disease in Gurkha infants every effort should be made to treat the peripheral circulatory collapse. It is suggested that intravenous transfusion with plasma, noradrenaline and cortisone would be a logical course together with the other usual supporting measures. In all cases, unconscious patients should be nursed in a position to prevent inhalation of vomit, which was a frequent terminal cause of death.

EPIDEMIOLOGY

The epidemiological study began in late February, 1956. A preliminary plotting out of the addresses of the series revealed that the distribution of cases, contrary to expectation, did not correspond to population concentration. The incidence over the years appeared to be confined to small, localised foci similar to the "islands" of transmission so characteristic of scrub typhus. This finding,

together with the rises in titre obtained in some of the cases with the OXK suspension used in earlier tests, led to the suspicion that the disease was a variant of infection with *Rickettsia orientalis*. As Lieut.-Colonel R. Traub, the officer in charge of the United States Army Medical Research Unit at Kuala Lumpur, was experienced in the epidemiology and control of scrub typhus, his aid was enlisted in carrying out rat-trapping and ectoparasite counts in the military foci of the disease.

In all cases a heavy rat infestation, with a relatively high trombiculid mite (*Trombicula deliensis* and *Euschöngastia indica*) index, was recorded. Blood-sucking mites, fleas and ticks were also found but not in such abundance. This apparent support of a scrub typhus hypothesis led to intensified mite control in military areas, the routine use of the Weil-Felix OXK agglutination test in all suspected cases and the trial of chloromycetin, especially in the more seriously ill.

Plotting of the addresses of civilian cases revealed the presence of many small foci in the city as well as in the rural areas. This occurrence of the disease in the centre of the city appeared to discredit the possibility of transmission by mites. However, a programme of intensive rat-trapping showed that the trombiculid mite, *E. indica*, could be found in large numbers even in the middle of built-up areas. The rat host in country districts was chiefly *Rattus diardi*, whereas in the town the latter was displaced at least in part by the brown rat *R. norvegicus*. The life cycle of *E. indica*, which is being carefully studied, allows for development either in scrub or in rat nests and burrows. Blood-sucking mites and fleas were more commonly found on the town rats.

Further information was obtained from a study of the year 1954, which was a serious year for both encephalitis and poliomyelitis. A comparison of the monthly incidence of the two diseases, which had previously been confused, shows that there is no apparent relationship between them (see Fig. 2). An interesting piece of circumstantial evidence to support the theory of mite transmission was given by the accidental infection of a soldier who slept in the room adjoining the laboratory in which rats were killed and the mites collected. He made a complete and rapid recovery.

In an attempt to control further incidence of the disease, all known foci within military areas were treated with insecticide. Dieldrin, because of its known efficacy against mites, fleas and mosquitoes, was used and all areas of scrub and grass were fogged with swing fog machines at a dosage of about 4 oz. dieldrin per acre. The control, as evidenced by the trombiculid mite index, appeared to last rather less than a month, so the process was repeated using the aerosol attachment of the machine, and applying the insecticide at an estimated dose of 10 oz. dieldrin per acre. This was repeated two months later when the mite index began to rise slowly, and the index fell and remained at almost zero for at least five to six months. Since the initial spraying, no cases have occurred within the military areas. However, Service cases continue to occur among families living outside garrison areas in civilian accommodation which invariably has been within known civilian foci. Cases continue to occur as before among the civilian population.

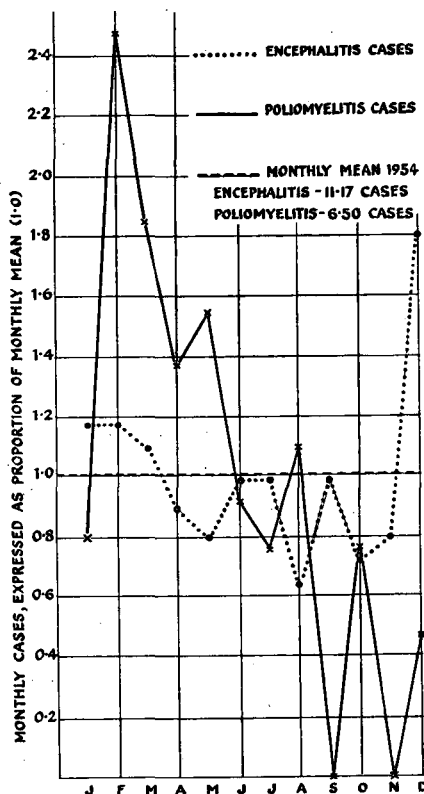


Fig. 2. Comparison of the monthly incidence during 1954 of poliomyelitis and encephalitis cases in Singapore

DISCUSSION

No attempt has been made in this preliminary report to discuss definitive diagnosis. In Singapore are found all the usual agents which can cause encephalitis (*e.g.* the viruses of mumps, measles, herpes, lymphocytic chorio-meningitis, the coxsackie virus and many others). Japanese B encephalitis is more specific to the Far East and was undoubtedly the cause of illness in some of the patients seen. However, the majority did not appear to fit into this virus group. If the disease described was due to any of the viruses of world-wide distribution already known to cause encephalitis, then it would be of considerable interest because of the frequency of clinical cases. From an epidemiological point of view and the types of illness encountered it seemed likely that the causal agent or agents would be found in the group of arthropod-borne viruses.

In view of this, the assistance of the U.S. Army Medical Research Unit in Kuala Lumpur was requested and was generously given. Through its Commanding Officer, Lieut.-Colonel Traub, M.S.C., a grant was obtained from the National Research Council for one of us (H. E. W.) to remain in Singapore for one year to work jointly with the U.S.A.M.R.U. collecting clinical material and suitable specimens for virus isolation and serological testing.

At present, with the complete co-operation of the General Hospital, Singapore, and the Service hospitals, the material from well over 100 patients is being studied by the U.S.A.M.R.U. They are attempting to isolate viruses from the post-mortem material collected, to test serologically for herpes, mumps, lymphocytic chorio-meningitis, glandular fever, leptospirosis, encephalo-myocarditic virus and Japanese B encephalitis. They are also testing the sera against any other agent or agents isolated by them from patients or possible vectors. Many of these results will shortly be made available.

At the time of writing, one of us (M. A. C. D.), who was in charge of the epidemiological study of the series, has been seconded to the World Health Organisation in Africa. However, routine collection of mosquitoes and mites and recording of other epidemiological data continue. Thus, if any new viral agent should be isolated or some more definite information be found regarding the vector, the data gathered will be invaluable in the further study of the disease.

It is hoped that this preliminary report will be of use to members of the Royal Army Medical Corps who come to Singapore and Malaya in the future, and that the investigation will continue until the aspects of this problem which remain obscure can be finally resolved.

SUMMARY

A brief description is given of the clinical and epidemiological aspects of a series of cases of encephalitis in Singapore. Virological and pathological study of material continues and a more detailed report will be issued at a later date.

Our thanks are due to many people whose co-operation made this investigation possible: these include the Director of Medical Services, FARELF, Brigadier Hennessey; Colonel Morrison, the Consulting Physician; Colonel Robinson, D.D.A.H.; Colonel Ross, A.D.M.S., Singapore Base District; Lieut.-Colonel Field, Assistant Director of Pathology, FARELF; Captain Brain, R.A.M.C.; Lieut. Hughes, R.A.M.C.; and the Statistical Department, G.H.Q. Singapore. Also we would like to express our appreciation of the valuable help given by Lieut.-Colonel Traub of the United States Army Medical Research Unit at Kuala Lumpur and his staff; the Government Health Department, the City of Singapore Health Department, and the staff of the Singapore General Hospital.