MURRAY VALLEY ENCEPHALITIS, 1974

CLINICAL FEATURES*

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Of the 58 patients who developed Murray Valley encephalitis (MVE) during 1974, 22 were admitted to Fairfield Hospital, Melbourne. The patients were of all ages, but the disease was most common in children. Calculations suggest that the incubation period of MVE is from one to four weeks. The severity of brain damage varies considerably; 11 patients recovered almost completely, seven had severe residual damage and four patients died. There are no special features which distinguish MVE from any other form of encephalitis. The survival of five of eight patients who required artificial respiration suggests that patients with suspected MVE should be transported at an early stage to a hospital where artificial respiration is available if necessary. There is no evidence that infection with the MVE virus can cause clinical manifestations of a disease other than acute encephalitis.

IN 1974 58 cases of Murray Valley encephalitis (MVE) occurred in Australia and 22 of these patients were admitted to Fairfield Hospital, Melbourne.[1] This aggregation of a comparatively large number of patients provided an opportunity to reappraise the clinical features of this disease.

EPIDEMIOLOGY

The epidemiological features of the 22 patients are shown in Table 1. The patients were admitted to hospital in the four-month period from January to May; most patients were admitted during February and March. With the exception of one (Case 2), all patients were infected in the Murray Valley area. Sixteen patients were indigenous to the place where they were infected and six were visitors to the Murray Valley district. The dates of travel were well documented for four visitors, and from these, incubation periods with upper limits of 10, 14, 17 and 28 days respectively can be calculated.

The ages of the patients ranged from three years to 74 years. Seven patients were aged 15 years or less. There was a preponderance of males over females (15: 7).

CLINICAL FEATURES

Most patients were admitted to hospital at an early stage of their illness. The factors contributing to this were an enthusiastic coverage by the news media and the modern tendency for country medical practitioners to refer patients with acute central nervous system infections quickly to a specialist hospital for investigation. Eighteen patients had had symptoms for only two to five days at the time of hospitalization and the remaining four had been ill for nine days, nine days, 20 days and 38 days respectively. Because of this early presentation it was possible to delineate the time sequence of the disease and divide it into two phases.

TABLE 1

Epidemiological Features of the 22 patients with Murray Valley Encephalitis

Case Number (Admission Order)	Age (years)	Sex	Area in Which Infection Acquired	Date of Onset of Symptoms (1974)
1	4	M	Barmah (Vic.)	January 10
2	15	M	Albury (N.S.W.)*	January 20
3	42	M	Mildura (Vic.)	January 14
4	71	F	Barnawartha (Vic.)*	January 24
5	67	F	Corowa (N.S.W.)*	January 10
6	60	M	Netherby (Vic.)	February 4
7	63	F	Murrayville (Vic.)*	February 12
8	7	M	Numurkah (Vic.)	February 9
9	60	M	Echuca (Vic.)*	February 13
10	42	F	Gerang Gerung (Vic.)	February 15
11	14	F	Manangatang (Vic.)	February 16
12	72	M	Nhill (Vic.)	February 19
13	60	M	Swan Hill (Vic.)	March 6
14	67	M	Toolamba (Vic.)	March 10
15	7	M	Mildura (Vic.)	March 12
16	74	M	Swan Hill (Vic.)	March 17
17	41	F	Horsham (Vic.)*	March 23
18	3	M	Cobram (Vic.)	March 25
19	55	M	Swan Hill (Vic.)	March 27
20	24	M	Katanga (Vic.)	April 4
21	21	M	Mildura (Vic.)	April 1
22	13	F	Jericho (Q.)	April 20

* Visitor to area.

Phases of the Disease

Prodrome

Earliest symptoms were non-specific and preceded features suggesting brain dysfunction. All patients had a history of fever, and an elevated temperature was recorded in the 20 who presented early. Fever usually lasted from four to 13 days (mean duration, eight days), though in one patient it persisted for 23 days till his death. The temperature chart of these patients had daily peaks of up to 40·6°C, a finding that is characteristic of many other types of encephalitis.

Seventeen patients complained of headache which was often frontal in site, and ten of nausea and vomiting. Four patients remembered a vague sensation of dizziness on the first day they became ill, two complained of muscular aches and two of photophobia during the first two days of their illness.

Features of Encephalomyelitis

Symptoms suggestive of disturbed brain function appeared in 16 patients within the first two days of the illness, within the first five days in five patients, but in one patient such symptoms did not become evident until the ninth day.

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Drowsiness and mental obtundation, which occurred in 12 patients, were the most common early features. Seven patients presented to their medical practitioners with confusion, disorientation, irrational or incongruous behaviour or inability to concentrate or to recognize relatives. Another early feature seen in six patients was ataxia, particularly a tendency to fall over. Various disturbances such as slurred or irrational speech, perseveration of speech and expressive aphasia were associated features in six patients. One patient developed urinary incontinence as an early symptom. Fitting was early evidence of brain disturbance in eight patients and in several this was observed to be *grand mal* in character.

By the time the patients were admitted to hospital several of the above-mentioned features were usually in evidence. Further neurological features then became apparent in those patients in whom the inflammatory process in the brain was progressive. Neurological signs often fluctuated from day to day, and in some patients even from hour to hour. Resultant findings presented many overlapping and variable patterns. For convenience of description the patients in this series have been arbitrarily divided into three groups according to the eventual clinical outcome of the disease.

Severity of the Disease

Mild

In Cases 4, 5, 6, 7, 11, 12, 15, 16, 17, 18 and 19, the disease was present in a mild form. Neurological involvement in the 11 patients was mild and recovery was virtually complete. Disturbed mentation was evidenced by drowsiness, disorientation, confusion, inability to concentrate, slow thinking, delirium and irritability. One patient became comatose and for a short period to time responded to painful stimuli only. Incoherent or slurred speech, expressive aphasia or speech perseveration occurred in some patients. Other disabilities experienced were general weakness, giddiness, ataxic gait and incontinence of urine.

The majority of patients in this group had neck stiffness and an intention tremor. Tremor was usually generalized, but in one patient it was restricted to the right hand and in another restricted to the tongue. Generalized limb hypertonicity was present in five patients, hyperflexia in four and ankle clonus in two. The plantar response was often equivocal, but in two patients it was extensor. By contrast, one other patient had hypotonic limbs. Repetitive aimless hand pleating of the bed clothes was observed in three patients.

Features which occurred less frequently were facial grimacing and twitching, grinding of the teeth, intermittent decerebrate posture and unilateral ptosis. One patient developed shallow respirations and required a period of artificial respiration. Another patient had a rash which consisted of purpuric spots on the thighs and chest and lasted less than two days. Neurological changes stabilized between the fifth and the tenth day of the illness and thereafter the patients' condition progressively improved.

The 11 patients in this category were discharged from hospital after periods varying from two weeks to three months, and most were reviewed at intervals up to 16 months after the onset of their illness. Seven patients made a complete recovery, but four had residual disabilities including emotional problems and mild degrees of impaired motor coordination and mental acuity.

Severe

In Cases 1, 8, 9, 10, 13, 20 and 21, the disease was present in a severe form. The seven patients were left with severe mental and/or physical disabilities. Their initial disease was similar to that of the patients with mild forms of the disease, but the eventual degree of central nervous system involvement was more profound.

Most of the patients had neck stiffness and an intention tremor. In three, the tremor was localized to the right side, to the tongue or to the face respectively. Other early features were ataxia, speech perseveration, expressive aphasia and pleating of bedclothes. There was progressive impairment of consciousness in all of the patients; four became comatose but responded to pain, and three were comatose but did not respond to pain.

Generalized limb hypertonicity and hyperreflexia were present in four patients. In two of the patients these symptoms subsequently changed to generalized limb flaccidity. Three patients initially developed flaccid paraplegia with lower limb areflexia. One of them had extensor plantar responses and in another the flaccid lower limbs later became spastic with extensor plantar reflexes. Four patients had extensor plantar reflexes and ankle clonus was observed in three.

Other changes observed included opisthotonus, generalized twitching, *grand mal* seizures, athetoid movements of the head and limbs, roving eyes and deviation of the eyes. Pharyngeal paralysis occurred in two patients and respiratory failure in five. Death would certainly have ensued in the latter patients without the use of artificial respiration.

All of the patients had severe residual disabilities including degrees of paraplegia or quadriplegia and various mental defects. In addition one patient had features of Parkinson's disease.

Fatal

Four patients, Cases 2, 3, 14 and 22, died which represented an 18% fatality rate. As in the severe cases the degree of central nervous system involvement in the patients was profound.

In three patients mental obtundation progressed to coma which was often associated with deviated eyes or rolling eyes or semipurposeful limb movement. Slight nystagmus was observed in only two patients. Initially all four patients had spastic quadriplegia, often with ankle clonus or extensor plantar responses; subsequently the quadriplegia became flaccid in two. Pharyngeal paralysis developed in one and respiratory failure in the other three, for which artificial respiration was given for variable periods.

Three patients had minimal central nervous system activity at the time of death. The other, although severely paralysed and in need of artificial respiration, remained conscious, but died from pneumonia and a *Candida albicans* fungaemia.

DIAGNOSIS

The cerebrospinal fluid of all but one of the 22 patients was examined (Table 2). They revealed non-purulent meningitis without specific diagnostic features. When the epidemic was well advanced, an encephalitic illness in association with a non-purulent meningitis in a patient who had recently been in the Murray Valley area was strong presumptive evidence for a diagnosis of MVE. Electroencephalograms performed on 15 patients revealed diffuse changes compatible with a diagnosis of encephalitis. Nevertheless in all patients relevant investigations were performed to eliminate the other causes of brain dysfunction in association with non-purulent meningitis and to confirm recent infection with MVE virus. It is interesting to note that the total blood white cell count (taken during the first week of the illness) was above 15,000/mm^3 owing to neutrophilia in eight patients. The highest value recorded was 24,000/mm^3.

Serological evidence consistent with MVE virus infection was obtained in all 22 patients[2] and the virus was isolated from the

brain in one of the fatal cases (No. 14).[3] Autopsies were performed on three of the four patients who died. Histological examination of tissue from the central nervous system showed the typical destruction of neurones in the spinal cord and brain stem and of the Purkinje cells in the cerebellum, which has been described by Robertson.[4]

TABLE 2

Cerebrospinal Fluid Findings

Case Number	Day of Illness	White Cell Count		Red Cell Count (/mm³)	Protein Level (mg/100ml)	Sugar Level (mg/100ml)
		Total (/mm³)	Polymorphs			
1 ..	6	42	29%	1	55	79
2 ..	4	270	27%	36	90	62
3 ..	11	23	5%	8	85	101
4 ..	7	11	25%	29	45	108
5 ..	21	20	60%	1	50	67
6 ..	5	750	60%	650**	170	69
7 ..	3	380	21%	30	100	59
8 ..	6	120	41%	10	105	63
9 ..	3	34	14%	17,500**	110	98
10* ..	4	38	20%	—	100	—
11 ..	5	540	17%	1,280**	135	55
12 ..	4	241	55%	6	110	74
13 ..	7	34	58%	—	120	52
14 ..	6	20	56%	720**	60	81
15* ..	3	64	10%	—	37	104
17 ..	5	175	20%	6	35	55
18 ..	4	200	60%	20	40	111
19 ..	5	125	85%	1,020**	90	85
20 ..	4	114	55%	1,800**	90	74
21* ..	6	365	23%	20	10	81
22* ..	3	17	60%	9	23	61

* Tests not performed at Fairfield Hospital.
** Traumatic Tap.

TREATMENT

Seventeen patients were treated with corticosteroids for variable periods to alleviate probably raised intracranial pressure. A tracheostomy was required in eight patients to ensure an adequate upper airway. Artificial respiration, usually by a tank respirator, was administered to eight patients for variable periods; one of these had a mild case and four cases were classified as severe.

Various antibiotics were administered to 17 patients either as a prophylactic measure or to treat complicating bacterial infections. The infections included two instances of Gram-negative septicaemia, three of urinary tract infection and four of pneumonia. Another patient developed a pulmonary embolus and recovered after suitable anticoagulant therapy.

THE POSSIBILITY OF NON-ENCEPHALITIC DISEASE DUE TO MVE VIRUS INFECTION

During the four-month epidemic period, 57 other patients who had been in the Murray Valley during the previous one to four weeks were admitted to Fairfield Hospital. Of these 39 were visitors to the valley and 18 were idigenes. Serological testing for MVE virus was performed on 43 patients, and of these, 24 who had a neurological disease were the only patients to show evidence of MVE virus infection. Details of these serological test results have been presented elsewhere.[2]

Two patients had encephalitis which was indistinguishable from MVE, but had no serological evidence of MVE virus infection. Two other patients, one with a cerebral tumour and the other with polyneuritis, had high stationary titres of MVE virus antibodies. The remaining 20 patients had aseptic meningitis and from 12 an enterovirus was isolated (from the cerebrospinal fluid in five). Three other patients with aseptic meningitis had low titres of MVE virus antibodies detected during the first nine days of their illness.

There was, therefore, no evidence that MVE virus can cause a non-encephalitic illness. Unfortunately follow-up antibody studies were not performed on the small number of patients who had aseptic meningitis and low antibody titres.

DISCUSSION

Clinical experience with MVE at Fairfield Hospital in 1974 confirms that this type of acute encephalitis has no special features which would allow it to be clinically distinguished from the other viral encephalitides which are common overseas,[5] or from many cases of herpesvirus hominis encephalitis. Microscopic and biochemical investigation of the cerebrospinal fluid of affected patients gave non-specific results. These conclusions were demonstrated by the two patients with an acute encephalitis possibly contracted in the Murray Valley area who were considered initially to have MVE until this diagnosis was negated by results of serological investigations.

Murray Valley encephalitis can occur at any age, but it is most common in children, possibly because a greater percentage of adults have developed an immunity from past subclinical infection. Calculations from the travel dates of four of the visitors to the Murray Valley area suggest that the incubation period is between one and four weeks, which is similar to the conclusion reached by Anderson.[6] After a prodromal period which usually lasts from two to five days and consists of fever, headache, nausea, vomiting and non-specific dizziness, clinical features of meningitis and brain dysfunction became apparent. The degree of brain damage varies considerably from patient to patient, and usually neurological signs become stable or begin to improve after the tenth day of the illness.

One half of the patients had mild encephalitis and they recovered almost completely. Seven other patients were left with severe residual physical and/or mental defects and four patients died. Murray Valley encephalitis has always had a high mortality. In the series described by Anderson,[6] 17 (42·5%) of the 40 patients died. In the 1974 epidemic 12 (20%) of the 58 patients died and four (18%) of the 22 of these patients who were admitted to Fairfield Hospital died. At this time there are no antiviral agents of proved value, particularly against arbovirus encephalitides. The administration of corticosteroids during the acute phase of the illness to reduce brain oedema and possibly to minimize any immunological mechanisms which might occur with the disease seems advisable. Antibiotics are usually required for prophylactic purposes or to treat secondary bacterial infections which often occur in patients with severe brain damage who require other forms of treatment to maintain life. Five of the patients would not have survived without artificial respiration; one of these patients completely recovered whilst the other four were left with severe residual defects. On this experience and in view of the possible rapid progression of the disease, all patients with suspected encephalitis, particularly MVE, should be transferred to a hospital with adequate facilities for the management of patients with respiratory paralysis.

It is interesting that infection with MVE virus has never been confirmed to cause clinical disease other than encephalitis. During the period of the 1974 epidemic, 20 patients who acquired aseptic meningitis in the Murray Valley area were admitted to Fairfield Hospital. In five of the patients the disease was shown to be due to an enterovirus and in seven a similar cause was considered likely. In none of the patients was there any serological evidence of recent MVE virus infection.

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ISOLATION OF MURRAY VALLEY ENCEPHALITIS VIRUS FROM THE BRAINS OF THREE PATIENTS WITH ENCEPHALITIS

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Murray Valley encephalitis virus was isolated from the brains of three patients who died from encephalitis during the 1974 epidemic. Isolation of the virus from autopsy material was successful when death occurred within two weeks of the onset of illness; however, no isolations were made from specimens collected before death or from autopsy material obtained from patients who died more than two weeks after the onset of symptoms. The virus was recovered most frequently in embryonated eggs, but two strains were isolated in cell culture.

THE AETIOLOGICAL AGENT of Murray Valley encephalitis (MVE virus) was isolated from brain specimens obtained at autopsy from four patients who died during the 1951 epidemic.[1 2 3] The virus was recovered from the cerebral cortex, basal ganglia, pons, medulla oblongata and cerebellum, but never from the cerebrospinal fluid (CSF), pharynx, lungs, blood or bowel contents.

The first isolates were obtained in newborn mice, which, after intracerebral inoculation, developed signs of encephalitis within five to six days and usually died a day or two later. The virus was also isolated in embryonated chickens' eggs where it produced a characteristic effect (small white pocks on the chorioallantoic membrane, death of the embryo and subcutaneous haemorrhages around the head, wings and feet).

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Since the 1951 epidemic, there have been two further reports of the isolation of MVE virus from man. Both were obtained from autopsy brain tissue from patients with encephalitis, the first a Papuan native who died in Port Moresby in 1956,[4] the second a young white woman who died in Queensland in 1969.[5] Although only six isolations of MVE have been recorded from man, the virus has been recovered from mosquitoes on several occasions[6] and recently from chickens.[7]

In this paper we record the isolation of MVE virus from three patients who died of encephalitis during the 1974 epidemic.

CLINICAL DETAILS

During 1974, 22 patients with Murray Valley encephalitis were admitted to Fairfield Hospital for Communicable Diseases, Melbourne.[8] Four of these patients died and autopsies were performed on three. In addition, autopsy material was available from two patients who died in Geelong and Ballarat respectively. The clinical histories of the first three cases are described in detail elsewhere[9] and the main features of all five cases coming to autopsy are summarized in Table 1.

LABORATORY INVESTIGATIONS

Several portions of brain were obtained aseptically from each patient and forwarded to the laboratory. Material from the two patients who died in country centres was received in sealed glass bottles packed in dry ice. All specimens were stored at −70°C until they could be processed.

The frozen specimens were ground in separate sterile mortars and 10% suspensions were prepared in Hank's balanced salt solution containing 40 units of neomycin per millilitre. The

TABLE 1

Details of the Patients from Whom Virus Isolation was Attempted.

Patient	Age (years)	Sex	Place of Infection	Date of Onset of Illness	Date of Death	Date of Autopsy	Haemagglutination Inhibition (HI) Antibody Titre Before Death
Case 1	10	M	Culgoa, Victoria	17.2.74	28.2.74	28.2.74	28.2.74, 1: 2560
Case 2	69	M	St Arnaud, Victoria	23.2.74	3.3.74	4.3.74	1.3.74, <1: 20
Case 3*..	67	M	Toolamba, Victoria	10.3.74	16.3.74	18.3.74	15.3.74, 1: 80
Case 4*..	42	M	Mildura, Victoria	14.1.74	6.2.74	7.2.74	6.2.74, 1: 80
Case 5*..	15	M	Albury, N.S.W.	20.1.74	20.3.74	22.3.74	15.3.74, 1: 40

* Patients 14, 3, and 2 described by Bennett.[9]