Western Equine Encephalitis in Infants

A Report on Three Cases with Sequelae

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• Approximately one-third of the laboratory-confirmed cases of Western equine encephalitis occur in children under the age of 10. The present paper describes three instances of Western equine encephalomyelitis virus infection in infants under one year of age, together with the resultant sequelae. The difficulties associated with diagnosis of central nervous system disturbances in very young children are discussed, and it is pointed out that in view of the frequent occurrence of clinical infections with the arthropod-borne encephalitis viruses these agents should be given serious consideration as a cause of acute central nervous system infection in childhood and as the possible etiology for obscure, severe neurological disturbances in the pediatric age groups.

SINCE THE ISOLATION and identification of the Western equine encephalomyelitis virus from horses by Meyer in 1931[6] and the development of serologic methods for determining the etiologic factor in cases of human infection, much epidemiologic information on the disease has accumulated. It has become apparent that in California this virus, as well as that of St. Louis encephalitis, is a frequent cause of the clinical entity "infectious encephalitis"[5] and that the geographical and seasonal distribution of human cases of Western equine encephalitis seems to be directly related to the environmental requirements of the arthropod vector, the mosquito Culex tarsalis.[4]

In the eight-year period 1945 through 1952, 1,985 cases of "infectious encephalitis" were reported to the California State Department of Public Health.[1] The year of highest incidence was 1952 with a total of 752 cases reported. In the seven years 1945-1951, 196 cases of Western equine encephalitis were confirmed by laboratory means, and in the year 1952 alone there were 370 laboratory proved cases (Table 1).

Epidemiologic studies of the laboratory-confirmed cases of virus encephalitis in California indicated that this disease is particularly frequent in the younger age groups. Lennette and Longshore[5] reported that of a total of 135 cases of St. Louis encephalitis occurring between the years 1945 and 1950, 38 (28 per cent) were in persons under 10 years of age, and 31 (40 per cent) of 77 cases of Western equine encephalitis were in persons in that age group. In 1952, of a total of 370 laboratory-confirmed cases of Western equine virus infection, 178 or 48 per cent were in persons under the age of 10 years. The proportion of cases of Western equine encephalomyelitis for the period 1945 through 1952 in which the patient was under 10 years of age is shown in Table 1. More than one-third of the laboratory-confirmed cases since 1945 have been in persons under the age of five years and approximately one-half in persons under the age of 10. Patients with St. Louis encephalitis in the same period were not of the younger age groups in so high a proportion of cases. It was suggested[5] that one reason for this might lie in a higher incidence of inapparent infection with the St. Louis virus in the general population of the endemic area which in turn could result in a high proportion of infants with passively acquired immunity.

While the severity of a disease may be reflected in the mortality rate, it may also be reflected in the development of serious sequelae which, over a period of time, may present highly important socio-economic problems. The incidence of sequelae in instances of human infection with the virus of Western equine encephalitis cannot be stated at present. This information will be acquired only after long-term study of large numbers of patients with labora-

TABLE 1.—*Age distribution of laboratory-proved cases of western equine encephalitis. California, 1945-1952*

Age Group	1945-50 No. Cases	1945-50 Per Cent of Total	1951 No. Cases	1951 Per Cent of Total	1952 No. Cases	1952 Per Cent of Total
Under 5 years.....	61	35	12	55	147	40
Under 10 years....	77	44	13	59	178	48
Total, all ages....	174	100	22	100	370	100

Source: California State Department of Public Health.[1]

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tory-confirmed infection. Such studies are at present in progress under the aegis of the California State Department of Public Health. Undoubtedly there are many instances of illness due to this virus in which the clinical symptoms are not those of an encephalitic process and laboratory confirmation therefore is not obtained. Until such time as the more common use of serologic tests in such cases brings to light the varied potentialities of the clinical syndrome of infection with this virus, the true incidence of sequelae will be difficult to ascertain. It is apparent, however, from the literature, that there occurs an appreciable incidence of serious neurological damage in children following viral encephalitis of several etiologic types, including that due to the Western equine virus. Wynns and Hawley,[9] dealing with St. Louis encephalitis, reported a mortality rate of 62 per cent in children, with neurological sequelae present in 22 per cent of the survivors. They noted that the incidence of permanent sequelae was highest in the younger age groups. Farber and co-workers[3] described eight cases of Eastern equine encephalitis in infancy; five patients died and the three survivors had permanent neurological sequelae. Simpson and Meiklejohn[8] examined 38 patients who had had Japanese B encephalitis one year after onset of the disease and noted sequelae in 11 of them, 10 of whom were under the age of 15 years. Reports of residual neurological damage following infection with Western equine encephalitis virus have been limited to descriptions of specific cases. Davis[2] reported two cases in early infancy with permanent sequelae in both. Noran and Baker[7] described one case occurring at the age of one month, with permanent neurological damage of severe degree and death at the age of three years.

It is the purpose of the present report to present three instances of permanent and serious neurological sequelae of Western equine encephalitis virus infection occurring in children under one year of age. The three patients were studied at the University of California Hospital and the diagnosis was confirmed by laboratory tests at the Viral and Ricksettsial Disease Laboratory of the California State Department of Public Health in Berkeley.

CASE REPORTS

CASE 1: A 10-month-old girl was admitted to the University of California Hospital on October 6, 1949, with complaints of convulsions and high fever for eight weeks. At the onset of illness mild diarrhea developed, and on the second day of illness, fever, as high as 108 degrees F., which continued for ten days. On the second day of fever, convulsion that lasted 24 hours occurred. The patient was then treated in a hospital for a week. At the time of discharge she was mentally disoriented and the right arm and right leg seemed weak. Fever continued and convulsions occurred at least once a day. A variety of diagnoses had been considered, including tonsillitis, infection of the ear, measles and pneumonia. The convulsions were ascribed to the fever.

TABLE 2.—*Results of laboratory tests on patient in Case 1, a girl, 10 months of age

Test Antigen	Type of Test and Results: Complement Fixation	Neutralization	Hemagglutination-inhibition
Western equine encephalitis	< 1:8	300 LD_{50} or >†	.....
St. Louis encephalitis	< 1:8	.....	.....
Mumps	.....	.....	1:16‡
Q fever	< 1:8	.....	.....

*Onset of illness in July 1949; blood specimen examined taken on October 7, 1949.

†Serum neutralized 300 or more 50 per cent mouse lethal doses of virus—a high titer.

‡Not diagnostically significant.

The family had been living in an agricultural community in Yolo County during the six months preceding the onset of illness.

The child, on admittance to the University of California Hospital, had a high pitched cry and her back hyperextended. The hands were clenched in tetanic fashion. Reflexes were equal and hyperactive. Babinski's reflex was evoked bilaterally.

The numbers of cells in the blood were within normal limits. The sedimentation rate was zero. No abnormalities were noted in the urine. The spinal fluid pressure was 20 cm. of water. No cells were observed in a specimen of spinal fluid and results of chemical studies were normal. The result of a toxoplasmin skin test was negative. Specimens of blood from the mother and infant for examinations for toxoplasmosis were sent to the Army Medical Service Graduate School in Washington, D. C., and were reported as "negative."* Specimens of blood from the patient were also sent to the California State Health Department's Viral and Rickettsial Disease Laboratory in Berkeley for study. The results of the viral tests are summarized in Table 2. The patient's blood had the capacity to neutralize 300 or more lethal doses of the Western equine encephalomyelitis virus. No blood could be obtained from the patient's mother for testing to rule out completely the possibility that the antibody in the child had been acquired by transplacental passage. While antibody titers of this magnitude have been observed by one of the authors (E.H.L.) in adults residing in areas where Western equine encephalomyelitis virus infections are endemic, it seems unlikely that passively acquired antibody would be present in such strength after 10 months. It is considered reasonable, therefore, to relate the child's antibody titer to the present illness. The fact that no complement-fixing antibody was demonstrable is not necessarily at variance with such an interpretation, since large-scale studies now under way in the Viral and Rickettsial Disease Laboratory show that complement-fixing antibody may appear quickly, reach a peak rapidly, and then decline or disappear after a variable, but brief, period.

No abnormalities were noted in x-ray studies of the chest. A pneumoencephalogram showed the ventricles to be symmetrically dilated, without displacement or block. The changes observed were ascribed to atrophy of the brain.

The temperature ranged between 37 degrees C. and 39 degrees C. and gradually became more stable around 37 degrees C. Episodes of spasms and convulsions became less frequent. At the time of discharge from the hospital, October 20, 1949, the patient seemed to respond to the voice of her parents and the nurses.

Psychometric studies carried out before discharge showed

*The authors are indebted to Dr. Joel Warren for conducting these tests.

a mental age of 6 months, and an intelligence quotient of 56. The child was socially responsive but did not voluntarily attempt to reach for moving articles. The psychometric studies were repeated six months after discharge, approximately eight months from the onset of disease. At this time the child showed a great deal of improvement in understanding words and in designating familiar objects. She was graded as approximately one year in mental age, representing a six-month gain in mental age in the interval since discharge.

The child was referred to the Cerebral Palsy Program through the Crippled Children's Service of the California State Department of Public Health and was accepted for aid.

Second admittance to hospital. The patient was admitted to the hospital March 17, 1952, referred from a hospital in the Central Valley where she had been hospitalized because of persistent convulsions of "unknown etiology." The child had continued to show improvement. She was able to close and open her hands but seemed to have difficulty in releasing objects. She was able to move her arms with poor control—the left better than the right. She could move both legs, the left better than the right, but was unable to walk. She was unable to sit up. There was some control over bladder and bowel function. She had difficulty in chewing but none in swallowing. She was able to say a few words, but no sentences.

The head was extremely small—45 cm. in circumference. There was asymmetry of the right occiput. Flexion spasticity of both arms was noted. The reflexes were normal. There was spasticity of the right leg. The feet were held in equinus position.

Electroencephalograms showed no dysrhythmia or focal change. Pneumoencephalography on March 19, 1952, showed well-filled ventricular system and subarachnoid channels, without displacement. The lateral ventricles and subarachnoid channels were larger than normal but relatively less so than in the pneumoencephalogram taken in October, 1949.

The procedure was done with the patient under ether anesthesia. Following removal of spinal fluid and introduction of air, cardiac and respiratory activity ceased.

Postmortem examination was carried out at the Coroner's office, City and County of San Francisco.*

There was foamy blood in the right ventricle and right auricle of the heart. The brain appeared edematous. Air bubbles were seen throughout the leptomeningeal vessels. On palpation firm, ill-defined nodules were noted in the gray matter, most prominent in the left mid-cortical region. There was thickening of the floor of the left lateral ventricle and adhesive bands in the third and fourth ventricles. Multiple sections revealed firm, pale sclerotic areas measuring 1 to 2 cm. in maximum diameter in both basal ganglia, in the subcortical white matter of the left parietal lobe, and in the right temporal lobe. There was disruption of the normal architecture of the pons. The cerebellar hemispheres showed pronounced sclerotic involvement of the white matter and the dentate nuclei. The spinal cord was macroscopically normal.

Upon microscopic examination, scattered small areas of degeneration and glial proliferation were observed throughout the cerebrum. In some areas perivascular lymphocytic reaction was present. Focal accumulations of macrophages were observed in areas of a basophilic staining material, presumably calcium. In the cerebellum some loss of Purkinje cells was noted. There was congestion in the brain stem and spinal cord.

CASE 2: The patient, a boy one month of age, was first admitted to the University of California Hospital July 6, 1950, with complaint of muscular spasms for the past 36 hours.

The illness had begun with the appearance of irritability and diarrhea. About 12 hours after onset of diarrhea, the child became rigid, with arms flexed and legs hyperextended. This lasted for several minutes. Similar episodes occurred frequently despite sedation. There were no clonic movements, no periods of apnea, and no cyanosis. The temperature fluctuated between 102 degrees F. and 104 degrees F. On the afternoon before admittance, a single dose of streptomycin was given on the assumption of a diagnosis of meningitis, due to *Hemophilus influenzae*. Leukocytes at that time numbered 8,000 per cu. mm. of blood.

The child had lived in Merced County before admittance to the hospital.

Upon physical examination the patient was observed to be lying limp and with the head turned to the right. The neck and back were not stiff. The reflexes were normal. The diagnosis on admittance was meningitis of unknown cause, probably bacterial.

Leukocytes numbered 7,600 per cu. mm. with 80 per cent polymorphonuclear cells. No growth occurred on cultures of the blood.

The spinal fluid was faintly turbid and contained 270 cells per cu. mm., of which 54 per cent were lymphocytes. The reaction to a Pandy test was 3 plus; the glucose content was 52 mg. and the protein content 150 mg. per 100 cc. No organisms grew on a culture of the fluid.

The results of serological tests for neurotropic viruses are given in Table 3, which shows that antibodies against Western equine encephalomyelitis virus appeared during the illness. No antibody was detected in the mother's blood, which indicates that the patient acquired antibody through active infection, and not passively from the mother.

The temperature ranged between 38 degrees C. and 39 degrees C. for the first five hospital days, following which it remained normal. A second specimen of spinal fluid was aspirated on the third hospital day. The leukocyte content was 370 per cu. mm., 90 per cent of which were lymphocytes.

By the sixth hospital day, the convulsive episodes had become less frequent and by the 16th hospital day the patient seemed considerably improved. Fluid withdrawn by cisternal puncture contained 30 cells per cu. mm., all lymphocytes; the protein content was 136 mg. per 100 cc. The patient was discharged.

Psychometric examination when the patient was two months of age showed development to a stage considered normal for infants 4 to 8 weeks of age. The results indicated definite improvement over examination shortly after admittance to hospital.

The child was examined again five months after the onset of illness and development was almost normal in all areas but gross motor abilities. There was a distinct interference in coordinated activity of arms and hands.

Upon physical examination 11 months after the illness, hyperactivity of reflexes of the left leg was noted. There was tension of the hands, in which effort seemed to impair achievement in picking up objects. A psychometric examination showed adaptive behavior at a level of 28 to 32 weeks, language behavior at 28 weeks, and personal-social behavior at 28 to 32 weeks. At a chronological age of 12 months, the development quotient was approximately 60.

The patient was admitted again on October 4, 1951. The complaint was a convulsion the day before admittance. This convulsion seemed to progress from left cheek to the left leg, and eventually included the whole body. There was moderate cyanosis. The episode lasted approximately four hours.

The patient was well-developed and well-nourished but seemed tired and irritable. The head was 43.5 cm. in circum-

*The authors are indebted to Dr. Henry Moon for permission to present the pathologic findings.

TABLE 3.—*Results of laboratory tests on patient in Case 2, a boy, 1 month of age, and on patient's mother*

Type of Test	Dates on Which Blood Specimens Were Taken and Results of Tests				
	Patient*				Mother of Patient
	July 11, 1950	July 21, 1950	Aug. 3, 1950	Oct. 5, 1951	July 28, 1950
Complement fixation					
Western equine encephalitis	< 1:8	1:64	1:256	1:64	< 1:8
St. Louis encephalitis	.....	< 1:8	< 1:8	< 1:8	< 1:8
Lymphocytic choriomeningitis	.....	< 1:8	< 1:8	< 1:8	< 1:8
Mumps	< 1:8	< 1:8	< 1:8	< 1:8	1:8
Neutralization					
Western equine encephalitis	400 LD_{50}	.....	5,000 LD_{50}	1,100 LD_{50}	Negative
St. Louis encephalitis	.....	.....	Negative	Negative	Negative

*Onset of illness July 4, 1950.

ference—small for a child 15 months of age. The reflexes were hyperactive bilaterally.

The diagnosis on admittance was postencephalitic convulsive state.

There were no cells in the spinal fluid, and glucose and protein contents were within normal limits.

Electroencephalography showed consistently higher than normal potential with greater abnormality on the right side of the head. These findings supported clinical evidence of a right hemispheric lesion. Upon pneumoencephalographic examination it was noted that the right lateral ventricle and third ventricle were slightly dilated. The subarachnoid channels on the right side were accentuated and enlarged. The impression was that of cerebral atrophy on the right.

Phenobarbital was administered, 15.0 mg. three times a day. Convulsive episodes occurred on two occasions, in each instance associated with fever of known cause.

The patient was examined again two years after the onset of the original illness. He was walking awkwardly and seemed to have a tightness in the left hand. Hyperactive and inattentive, he jumped about on the floor in a leapfrog fashion or banged objects noisily and gleefully responded to the racket. There was no interest in sustained or associative play. Upon psychometric examination the mental development was observed to be that of a normal child about nine and a half months of age and the intelligence quotient was about 40.

Reexamination approximately two and one-half years after onset of disease showed no change from the previous study. By psychometric evaluation the child was determined to be at "imbecile" level of function. Application had been made for placement in an institution.

CASE 3:* A seven-month-old white girl was admitted to the University of California Hospital in December 1952. The complaint was convulsions.

In June 1952 the patient had had a temperature of 102.6 degrees F. and was moderately sick. There were no positive physical findings and no specific therapy was prescribed. The patient was examined again by the same physician the following day and, except for high fever, no definite symptoms or physical findings were noted. Two days later the baby suddenly had a convulsion. Lumbar puncture was carried out and the spinal fluid contained 1700 leukocytes per cu. mm. A diagnosis of encephalitis was made, principally on the basis of the increased incidence of the disease at the time and also because the parents reported that the child had been bitten by a mosquito shortly before the illness began. A horse on a neighboring ranch was known to have died of encephalitis in the previous month.

*This case is presented through the courtesy of Dr. George H. Schade.

TABLE 4.—*Results of laboratory tests on patient in Case 3, a girl, 7 months of age, and on patient's mother*

Type of Test	Dates Blood Specimens Taken, and Results of Tests		
	Patient*		Mother of Patient
	Dec. 22, 1952	Mar. 2, 1953	April 6, 1953
Complement fixation			
Western equine encephalitis	1:1024	1:512	< 1:8
St. Louis encephalitis	< 1:8	.....	< 1:8
Mumps	< 1:8	.....	< 1:8
Neutralization			
Western equine encephalitis	1 million LD_{50}	.....	100 LD_{50}

*Onset of illness June 30, 1952.

There were frequent major convulsive seizures for several days. Improvement was then rapid and the patient was considered well after seven days.

Thereafter the baby developed slowly. At about six months of age, she began to have sudden dropping movements of the head with sharp jerks of the arms and uprolling of the eyes. The mother said the baby did not seem alert.

On physical examination there was no evidence of abnormality of the head. The reflexes were normal, but the motor tone was poor. Moro reflex was equal and hyperactive. During the examination, several swift convulsive seizures of major intensity were observed.

Electroencephalogram showed both generalized and focal paroxysmal dysrhythmia of a wave and spike type. The focal change was in the frontal half of the right hemisphere. The interpretation was "severe cerebral dysfunction of the convulsive type." The abnormality noted was similar to that described in encephalitis of some types.

Psychometric examination showed development that would be normal at approximately six weeks of age, with a developmental quotient of 21. Virologic tests of the blood were carried out. The results are given in Table 4. Strong complement-fixation and an extremely high level of neutralizing antibodies to the Western equine virus were observed. The high titer of complement-fixing antibodies in the child, and absence of them in the mother, together with a neutralizing antibody level 10,000 times that found in the mother, indicated that the patient was actually infected with the Western equine virus, and did not acquire antibodies passively.

The diagnosis was postencephalitic convulsive state, with lightning major seizures and severe mental retardation.

DISCUSSION

The three cases described illustrate the severe neurological damage that may result from infection with the virus of Western equine encephalitis in early childhood.

In the first patient, the prolonged febrile period, lasting about eight weeks, suggests that prolonged fever may constitute a possible diagnostic clue in central nervous infection of this type. The persistent fever may also have contributed to the damage in the brain. The convulsions, which were initially ascribed to the high fever, also represent important diagnostic clues, which should be considered a definite indication for lumbar puncture. The improvement noted in the patient over a period of over two years is manifest not only in the psychometric tests but also in the comparison between the two pneumoencephalograms. Nevertheless, at the time of her death, which cannot be ascribed to encephalitis, she represented not only a serious problem for her immediate family but also a long-term problem for a number of public and private agencies. The pathological findings in this patient are of interest inasmuch as they are compatible with either a neurotropic virus disease or toxoplasmosis. The latter disease seems to be unlikely in view of the negative results of serological tests on both mother and infant and, in the patient, the negative reaction to a skin test and the normal optic fundi. Furthermore, the findings in the brain are essentially similar to those described by Noran and Baker[7] in a case of Western equine encephalitis as well as to those reported by Zimmerman[10] in cases of Japanese B encephalitis. The observation of focal sclerotic areas especially resembles the findings described by Zimmerman. The observation of deposits of calcium salts was reported by Noran and Baker and was stressed by Zimmerman. These investigators were describing material from cases in which, as in the present case, death took place long after the acute stage of disease.

Case 2 illustrates the problems of diagnosis that may be encountered in the early stages of the disease. In this case it seems quite possible that the short febrile period could have been ascribed to a successfully treated bacterial infection, in which the causative organism was not identified because an antibiotic was used before material for cultures could be obtained. The serological diagnosis in this case was enhanced by obtaining a blood specimen from the mother, which showed the absence of antibody. It was thus possible to assume that the antibody found in the specimen taken from the patient had been acquired since birth and not by passive transfer through the placenta. The pneumoencephalographic evidence of a focal destructive process correlated well with the clinical observation of early stiffness in one leg and of the nature of the convulsions. The child represents a very difficult problem for the parents to handle and will be under custodial care of the state indefinitely.

Case 3 also is illustrative of difficulties that obscure the diagnosis. The eventual solution resulted from the application of viral diagnostic tests in a case of "convulsions of unknown cause."

From the small amount of information available in the published literature, and with the cases here reported as further evidence, it appears that Western equine encephalitis may by no means be a rare cause of serious neurological damage in childhood. With the increased number of cases of human infection with this virus in 1952, and the expectancy that cases of this disease will continue to occur, physicians in California should give serious consideration to this virus, not only as a cause of acute central nervous system infection in childhood, but also as an explanation for obscure, severe neurological disturbances in the pediatric age groups.

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