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The 1952 Outbreak of Encephalitis in California

Differential Diagnosis

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• Clinical data adequate for analysis were available in 386 laboratory-confirmed cases of arthropod-borne encephalitis — 38 St. Louis and 348 western equine. Consistently observed symptoms varied with the age of the patient. Symptoms that occurred in a high proportion of patients in each age group were:

Less than one year of age: Fever and convulsions. (None had the St. Louis disease.)

One through four years: Fever, headache, vomiting, drowsiness, irritability, restlessness, nuchal rigidity, tremor, and sometimes convulsions.

Five through fourteen years: Headache, fever, and drowsiness. Sometimes the disease progressed no further, but if it did, nausea, vomiting, muscular pain, photophobia and limitation of neck and back flexion often were noted; and sometimes convulsions and intention tremors.

Fifteen years and older: Drowsiness, lethargy, malaise, fever, stiffness at the back of the neck and, almost always, severe intractable occipital headache associated with nausea, disturbance of vision, photophobia and vertigo.

The extreme difficulty of differential diagnosis on the basis of clinical observation was indicated by the wide range of diagnoses made in these cases before the invading organism was identified by laboratory studies.

THE PURPOSE OF THIS PAPER is to present the clinical characteristics of the arthropod-borne encephalitides as observed during the 1952 outbreak in the Central Valley of California. The objective is to set forth the salient clinical features of the so-called "typical case" and to point out the features less commonly associated with this disease. The problems in the differential diagnosis have been commented on by others.[2, 5, 9, 10, 18, 19]

The analysis of clinical material is based on 792 reported cases of acute infectious encephalitis for the period June to October, 1952. Particular attention is given to 386 laboratory confirmed cases of arthropod-borne encephalitis on which adequate clinical information was available for analysis. Of the 386 cases in which the etiologic factor was determined and there were adequate clinical data, 348 were caused by western equine virus and 38 by St. Louis virus.

The serological tests and viral isolations were performed by the Viral and Ricksettsial Disease Laboratory of the California State Department of Public Health. The etiologic factor was considered established when significant rises in titers of either complement-fixing or neutralizing antibody or both,

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LABORATORY CONFIRMED CASES OF WESTERN EQUINE AND ST. LOUIS ENCEPHALITIS, PERCENT IN EACH AGE GROUP MANIFESTING SELECTED CLINICAL SIGNS AND SYMPTOMS CALIFORNIA, 1952

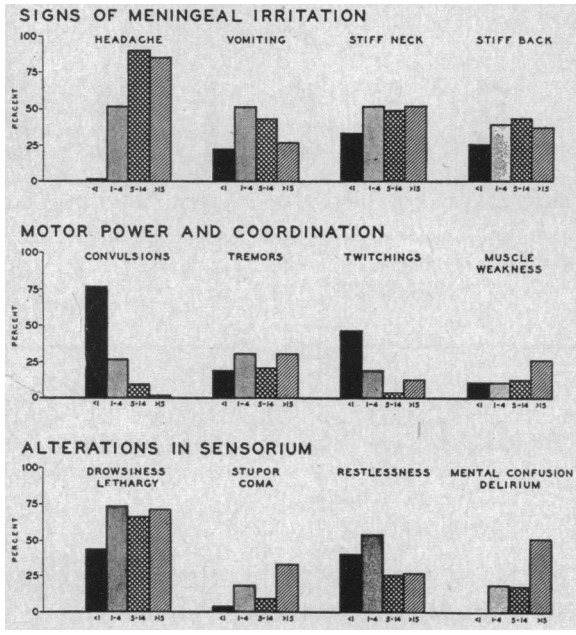

CHART 1

were demonstrable, or when in fatal cases the virus was recovered from the brain.[16]

The available data were compiled from observations by epidemiological field teams, members of hospital staffs and practicing physicians. Because of the number and variety of observers, there were difficulties in obtaining complete, consistent and comparable clinical data on this group of proven cases.

Detailed epidemiological data are given in a paper by Hollister and co-workers.[14] However, it should be pointed out that there was wide variation in the ages of patients and the ability to elicit subjective and objective symptomatologic information varied with age groups. It was felt, therefore, that a discussion of the clinical features should be considered by age groups. The four divisions that have been made are as follows: Infants less than 1 year of age, infants and children 1 through 4, children 5 through 14, and patients 15 years of age and over. Clinically the western equine and St. Louis types have much in common[8, 10, 17] and, therefore, they will be discussed together.

CLINICAL FINDINGS

All cases in infants less than one year of age were caused by the western equine virus. In this age group the only consistently noted symptoms were sudden onset of fever accompanied by convulsions.

TABLE 1.—*Signs and symptoms of arthropod-borne encephalitis* by age group*

	Under 1 year	1-4	5-14	15 and over
Total cases	94†	52†	53†	187†
Signs and Symptoms	Per cent			
Pyrexia	92	81	94	91
Less than 100° F.	1	4	6	4
100-101.9	5	6	9	7
102-103.9	38	38	53	39
104 and over	48	33	26	41
Not stated	8	19	6	9
Signs of meningeal irritation				
Headache	1	52	91	87
Nausea	1	22	30	30
Vomiting	22	52	43	27
Stiff neck	33	52	49	52
Stiff back	25	39	43	36
Alterations in sensorium				
Drowsiness	36	67	59	66
Lethargy	26	54	42	51
Malaise	5	31	34	40
Stupor	2	14	6	28
Coma	2	8	4	13
Restlessness	40	54	25	26
Mental confusion	....	17	15	44
Delirium	....	8	6	14
Motor power and coordination				
Convulsions	77	27	9	1
Tremors	19	29	20	29
Twitchings	47	19	3	12
Muscle weakness	10	10	11	26
Dysarthria	....	8	....	7
Ocular signs or symptoms				
Strabismus	1	4	4	6
Diplopia	....	4	4	8
Blurred vision	....	....	2	5
Photophobia	....	14	8	12
Conjunctivitis	1	2	2	6

* Proved cases of western equine and St. Louis encephalitis.
† Number of cases in each group.

(There was no history of antecedent complications at delivery or in the neonatal period.) It was observed that while the convulsions were frequently generalized, they often were focal, involving one or both of the upper or lower extremities. Typically, the fever ranged between 102° and 104° F., rectally during the course of illness, but frequently the maximum was over 104° F. The temperature remained high despite chemotherapy. Findings related to tenseness of the fontanel, abnormality of reflexes, and degrees of rigidity of extremities were difficult to evaluate and could not be relied upon to aid in the diagnosis. The consistent observations in this age group were fever (in 92 per cent of cases) and convulsions (in 77 per cent) as shown in Table 1 and graphically in Chart I.

In the age group 1 through 4 years, the complaints of fever and convulsions were mentioned but were not typical characteristics. The history obtained on admittance to hospital usually indicated fever, headache, vomiting, drowsiness, irritability and restlessness of one to three days' duration. The

most consistent positive physical findings in these cases were fever, nuchal rigidity, and tremor (Table 1). Muscular weakness was observed in 10 per cent of the cases. In one case of western equine encephalitis, brain stem and cord involvement was indicated by absence of the gag reflex, facial paralysis and intercostal paralysis. Tracheotomy was necessary in that case. Within a period of nine months the child progressively recovered with no evident residual muscle weakness.

In the age group 5 through 14 years, subjective symptoms were more easily elicited (Table 1). Headache, fever and drowsiness often existed two to three days before admittance to hospital. In many instances the illness progressed no further and a definite diagnosis was made only because specimens of blood were examined. In cases in which the disease progressed, the previously mentioned subjective symptoms became more intense and were often associated with nausea, vomiting, muscular pain, photophobia and, less frequently, convulsions. These children were acutely ill, febrile and lethargic. Often there was limitation of flexion in the neck and back. Intention tremors were not infrequent and in one case the tremor was pronounced enough to suggest an initial diagnosis of Sydenham's chorea. Muscular weakness was observed in 11 per cent of patients and it persisted a week or longer. Tracheotomy was performed on one patient with western equine encephalitis in this age group because of bulbar and cervical cord involvement.

In patients 15 years of age or older, the initial complaints were "grippe-like," characterized by generalized malaise, drowsiness, lethargy, fever, tight or stiff sensation in the back of the neck, and intense headache of two to four days' duration as noted in Table 1. Headache was almost a universal symptom (86 per cent) and was commonly so severe as to dominate all subjective symptoms. The pronounced incapacitation caused by headache was frequently the sole reason adults sought medical attention. Typically, the headache was localized in the occipital region, was throbbing in character, and usually was not relieved by analgesic drugs, including narcotics. Movement, upright position or coughing often caused accentuation in the intensity of the pain. Phenomena associated with the headache included nausea, vomiting, blurring of vision, diplopia, strabismus, vertigo and photophobia.

Shortly after onset, the typical adult patient became mildly disoriented and drowsy and had signs of meningeal irritation. Tremors of intention type were not uncommon and were often rather coarse. Tremors involving facial musculature, including the lips, were rather frequently noted. In many cases the disease was mild and the patient was apparently well within a few days. Complete stupor developed in 28 per cent of the more severe cases, for the most part in patients in the higher brackets of the age group. Thirteen per cent of patients in this age group became comatose and were incontinent for three or four days or longer and finally recovered from this critical state. These observations are similar to those made by Adamson[1] in a study of cases in the Manitoba outbreak in 1941. Adamson emphasized that this is the only brain condition in which unconsciousness may persist for so long without being followed by death or gross disability.

There were three patients in this age group, two with western equine and one with St. Louis encephalitis, who had definite indications for tracheotomy. All three recovered, but the patient with St. Louis encephalitis had residual flaccid paralysis of the lower extremities of a known duration of eight months. Tracheotomy was also done in two cases in which encephalitis was diagnosed clinically but the results of laboratory tests were inconclusive.

LABORATORY DATA

Routine laboratory examination of urine and blood were of little diagnostic assistance in this study. The most common urinary finding was transient albuminuria. In examination of the blood, neither leukopenia nor leukocytosis was consistently observed. Usually slight, transient leukocytosis was noted. Examination of the cerebrospinal fluid, while important as a diagnostic aid in central nervous system disease, showed wide variation in the total number of cells as well as in the differential count. Usually the total number of cells ranged from 50 to 200 per cubic millimeter with polymorphonuclear leukocytes predominating early. Lymphocytes were more numerous later in the course of the disease. In infants the cerebrospinal fluid showed a greater degree of pleocytosis than was observed in older patients. Fifty-one per cent of infants less than one year of age had spinal fluid cell content of more than 300 per cubic millimeter and 31 per cent had more than 500 per cubic millimeter. Sugar and chloride values in all age groups were normal and the protein content was either normal or slightly to moderately elevated.

The most important aspect of the virus laboratory examination is the demonstration of a rise in titer of either complement fixing or neutralizing antibodies in two or more serum samples taken in the acute and convalescent phase of the disease. (This is discussed in detail in a paper by Lennette and coworkers.[16]) In fatal cases, specific etiological diagnosis may be made by isolation of the virus from central nervous system tissue.

DIFFERENTIAL DIAGNOSIS

The experience with encephalitis in California in 1952 reemphasized the difficulties involved in establishing on clinical grounds a diagnosis of the arthropod-borne virus encephalitides. Table 2 shows the wide range in the initial diagnoses considered by the attending physicians in cases in which laboratory tests ultimately proved either western equine or St. Louis encephalitis. The outstanding clues that should at once arouse suspicion of either the western equine or the St. Louis virus as the etiologic agent are the dramatic seasonal incidence and the rather sharply defined area of endemicity of the two diseases.[14]

Clinical laboratory aids in diagnosis are essential to rule out other conditions in which there may be primary or secondary encephalitic components. Cerebrospinal fluid examinations, including cell counts, smears, cultures, animal inoculations, chlorides and protein determinations, as well as serologic tests are important in the exclusion of acute bacterial meningitis, acute syphilitic meningitis, tuberculous meningitis and coccidioidal infection of the central nervous system. In this regard, it is important to emphasize that in a large proportion of the cases in infants the content of cells in the spinal fluid noted in association with either of the two arthropod-borne encephalitides was similar to the cell content associated with bacterial infection. Thus, cell content of 500 or more per cubic millimeter does not rule out virus encephalitis.

A complete case history supplemented by physical and laboratory examinations will aid in ruling out such conditions as postinfectious encephalitis[13, 23] following mumps, measles and chickenpox, postvaccinal encephalitis,[6, 26] brain and cord tumors and abscesses, metabolic and general vascular disturbances, toxic encephalopathic conditions and miscellaneous conditions such as subacute bacterial endocarditis, ricksettsial involvement of the central nervous system[12] and Guillain-Barre syndrome.

Sometimes the arthropod-borne encephalitides can be differentiated from polioencephalomyelitis, but usually there is much difficulty in distinguishing between them.[3, 4, 11] Until a simple test for identification of the virus of poliomyelitis becomes available, its role as a causative factor in the many cases in which the infecting organism is not identifiable by present means, will remain obscure.[22] Both are likely to occur in the Central Valley of California during the summer and early fall months. In both conditions, onset with headache and fever is common.[25] However, sudden onset, occasionally fulminating, with high temperature usually indicates arthropod-borne encephalitis as the more likely.

Although development of paralysis or bulbar symptoms soon after onset is presumptive of poliomyelitis, it is important to keep in mind that these complications occurred also in laboratory-confirmed cases of encephalitis: Tracheotomy was necessary in five cases of proven encephalitis, four western equine and one St. Louis, in 1952.

TABLE 2.—*Initial diagnosis of diseases ultimately proven by laboratory test to be either western equine or St. Louis encephalitis*

Polioencephalomyelitis	Brain trauma
Bacterial meningitis	Brain abscess
Tuberculous meningitis	Cerebrovascular accident
Mumps encephalitis	Intracranial hemorrhage
Coccidioidal infection	Intracranial neoplasm
Lymphocytic choriomeningitis	Convulsive disorder
Central nervous system syphilis	Cardiac failure
Coxsackie encephalitis	Subacute bacterial endocarditis
Pneumonia	Sydenham's chorea
Otitis media	Diabetic coma

The variegated clinical manifestations in this group of diseases arises from the fact that any of them may affect any portion of the encephalon and myelon. Quong[20] in a study of 18 deaths in proven cases that occurred in a severe epidemic of western equine encephalitis in Manitoba in 1941, described in addition to brain lesions diffuse cord lesions which extended to both anterior and posterior horns.

Sulkin,[24] reporting on histopathologic observations in a fatal case in which the western equine virus was isolated, stated: "The inflammatory reaction was most apparent in the spinal cord, but involved the medulla, pons and midbrain to a striking degree. No inflammatory reaction was evident in the cerebrum, corpus striatum or cerebellum."

In the 1952 outbreak, Huntington,[15] pathologist at Kern General Hospital, observed lesions in the segments of the upper cervical cord in a number of confirmed cases.

In light of these pathologic changes, it is easier to understand the bulbar and lower motor neuron signs that are occasionally observed in the arthropod-borne encephalitides. These may result in flaccid paralysis of single extremities with absence of deep tendon reflexes, signs of involvement of cranial nerves or respiratory distress which may necessitate tracheotomy or the use of a respirator. In one case, there was a unilateral sensory loss over the area of distribution of the ophthalmic branch of the fifth cranial nerve.

DISCUSSION

As has been pointed out by a number of investigators,[7, 8, 17] it is impossible to differentiate western equine from St. Louis encephalitis clinically. Malodorous perspiration in cases of western equine encephalitis noted by Hammon[8] in his report on encephalitis in Yakima was of no differential diagnostic significance in the authors' experience. Final

diagnosis rests with the demonstration of a rise in titer of specific antibodies in the serum of the patient. Reeves[21] reported that 20 per cent of a "normal population" in an endemic area had neutralizing antibodies to St. Louis virus and 10 per cent had evidence of contact with western equine virus. Therefore, a single specimen of blood with neutralizing antibody has little diagnostic significance. Conversely, negative result of a test of a single specimen taken in the acute phase does not rule out the disease. Antibodies may appear at varying time intervals after the beginning of the illness with either western equine or St. Louis encephalitis. At least two specimens of serum are, therefore, necessary in order to show that antibodies have appeared or increased in titer during the course of the illness. The first specimen should be taken as early in the course of the disease as possible; the second, ten days or more after the first. Sometimes it is necessary to obtain a third, fourth or even fifth specimen to establish a diagnosis. Of note is the fact that in 34 of the cases in the 1952 epidemic there was no antibody rise until approximately 35 or more days after onset of illness.

It should be stressed that in addition to the 386 laboratory confirmed cases, there were 198 cases in the category of encephalitis, "etiologic agent not known." No antibody rise could be demonstrated to viruses of western equine or St. Louis encephalitis or mumps in a series of blood specimens. Results of tests, done later, of these negative specimens for antibodies of eastern equine, Japanese B, lymphocytic choriomeningitis and California viruses were also negative. Analysis of clinical signs and symptoms reported in this group shows them to be strikingly comparable to those observed in the "laboratory confirmed" group. This relationship, suggesting that as yet undiscovered etiologic agents may be responsible for the syndrome of encephalitis, has previously been described.[9, 17] Clarification of this problem apparently must await further epidemiologic studies, the development of better serologic tools to assist in establishing a specific etiologic diagnosis and, possibly, on the isolation of new etiologic agents.

In the event of death, postmortem examination is highly desirable, both for histopathological studies and for isolation of etiological agents from the brain and central nervous system tissue. On the basis of observation in the laboratory confirmed cases, it is well to reemphasize the value of the histopathological studies—not only of the brain and upper cervical cord that can be obtained through the foramen magna, but also of the entire cord.

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REFERENCES

1. Adamson, J. D., and Dubo, Sara: Clinical findings in encephalitis (western equine), Canad. Pub. Health J., 33: 288, June 1942.

2. Black, W. C., Agsher, W. K., and McDonald, J. G.: Epidemic encephalitis in Colorado, Rocky Mtn. Med. J., 42: 354, May 1945.

3. Buss, W. C., and Eaton, J.: Encephalitis in Kern County, California, 1941-1950, Calif. Med., 76:350, May 1952.

4. Clark, S. B., and Finley, K. H.: Some clinical aspects of the human arthropod-borne virus encephalitides in California as a diagnostic aid to physicians. Unpublished data.

5. Dingle, J. H.: The encephalitides of virus etiology, N.E.J.M., 225:1014, 1941.

6. Editorial: "Encephalitis Following Vaccination Against Pertussis," Ann. Int. Med., 32:343, Feb. 1950.

7. Finley, K. H.: Virus encephalomyelitides, The Med. Clinics of N. A., 37:373, March 1953.

8. Hammon, W. McD.: Encephalitis in the Yakima valley. Mixed St. Louis and western equine types, J.A.M.A., 117:161, July 1941.

9. Hammon, W. McD.: The encephalitides of virus origin with special reference to those of North America, The Med. Clinics of N. A., Vol. IV, No. 2, 1945.

10. Hammon, W. McD.: The epidemic encephalitides of North America, The Med. Clinics of N. A., May 1943.

11. Hammon, W. McD., and Reeves, W. C.: Interepidemic studies on arthropod-borne virus encephalitides and poliomyelitis in Kern County, California and the Yakima valley, Washington, 1944, Amer. J. Hyg., 46:326, Nov. 1947.

12. Harrell, G. T.: Rickettsial involvement of the nervous system, The Med. Clinics of N. A., 37:395, March 1953.

13. Hodes, H. L.: Common types of encephalitis in children, N. Y. State J. Med., 50:227, Oct. 1950.

14. Hollister, A. C., Longshore, W. Allen, Dean, B. H., Stevens, I. M.: The 1952 outbreak of encephalitis in California—Some epidemiologic aspects, Calif. Med., 79:84-90, Aug. 1953.

15. Huntington, R. W.: Personal communication to the authors.

16. Lennette, E. H.; Nyberg, Marjorie; Barghausen, Dolores; Chin, Roland; Fujimoto, Francis; Itatani, Margaret: The 1952 outbreak of encephalitis in California—Laboratory methods for etiologic diagnosis, Calif. Med., 79: 78-83, Aug. 1953.

17. Lennette, E. H., and Longshore, W. Allen: Western equine and St. Louis encephalitis in man, Calif. Med., 75: 189-195, Sept. 1951.

18. Medovy, H.: Western equine encephalomyelitis in infants, J. of Ped., 22:311, Jan.-June, 1943.

19. Price, A. H.: The meningitides and encephalitides, The Med. Clinics of N. A., Nov. 1943.

20. Quong, T. L.: The pathology of western equine encephalomyelitis, Canad. Pub. Health J., 33:300, June 1942.

21. Reeves, W. C.: Personal communication to the authors.

22. Rivers, T. M.: "Viral and Rickettsial Infections of Man," 2nd ed., J. P. Lippincott Co., 1952.

23. Sawchuck, S., LaBoccetta, A. C., Tornay, A., Silverstein, A., and Peale, A. R.: Measles encephalitis—study of fifty cases, Am. J. Dis. of Child., 78:844, Dec. 1949.

24. Sulkin, S. E.: Human encephalitis due to the western equine encephalomyelitis virus, Texas State J. Med., 41:455, Jan. 1946.

25. Tichy, F. Y., and Baker, A. B.: Acute anterior poliomyelitis, The Med. Clinics of N. A., 37:363, March 1953.

26. Winkleman, C. W., and Gotten, N.: Encephalomyelitis following the use of serums and vaccines, Amer. J. Syph. and Neurol., 19:414, 1935.