Neurological Complications to Treatment With Rabies Vaccine

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MANY physicians have been confronted with the problem of deciding when or when not to give a child bitten by a dog the series of anti-rabies vaccine injections. Fortunately, often the child or adult has been bitten by a family pet or neighbor's dog during a playful tussel. But what about the stray dog or cat, especially when it is subsequently not located for study by the health department? The wound site, depth, degree of tissue injury, and the time interval between the bite and its proper cauterization are the primary factors first to be considered. If in our judgment there is a chance of rabies developing, we proceed with the series of subcutaneous injections of rabies vaccine. However, some physicians have had or have read about local, central nervous system, or generalized reactions to the vaccine that may make them hesitate to initiate the series. For these and other reasons they may err in hazarding the patient's health by withholding the vaccine treatment because of lack of knowledge of the facts about rabies vaccine reactions.

Just what are the dangers in vaccine treatment against rabies? Have there been many cases here or elsewhere of complications to treatment? If so, how do these dangers compare with the chances of getting rabies? These and many other related questions prompted us to survey the files of the Los Angeles County Hospital of cases of rabies treatment reaction admitted over the last five years and report the findings on these cases and those from the literature to date.

In the five years, 1940 to 1945 inclusive, we found cases of complications of rabies vaccine treatment admitted to the contagious disease unit of the Los Angeles County Hospital. All five cases presented mainly a neurological clinical pattern and were true examples of complications due entirely to treatment with rabies vaccine. All five cases recovered.*

1. *Incidence, Morbidity and Mortality*

California is one of the leading states in the nation in incidence of animal rabies. The California State Department of Public Health *Bulletin* (June, 1946) reports a total of 911 cases of animal rabies in the state in 1944, and 581 in 1945. In 1944 California had almost 10 per cent of the total reported animal rabies cases in the country with onlv Texas and Louisiana reporting more cases. Of California's 911, Los Angeles County in 1944 had 730 cases, 80 per cent of the state's total or approximately 7 per cent of all the animal rabies cases in the United States!

During the five-year period covered by this paper (1940-1945 inclusive), in Los Angeles County there was a total of 2,167 cases of animal rabies reported with 2,389 people receiving the Pasteur treatment by the Los Angeles City and County Health Departments. Two of our cases* came from the health departments, representing an incidence of severe complications among this group of one per 1,194. If this is at all representative it is higher than that reported previously where incidence of complications varies from one per 3,688 treated (0.027 per cent)[6,8] to one per 6,250 treated (0.016 per cent),[5] with one author reporting an incidence as high as one per 1,200 (0.083 per cent).[4]

In Los Angeles County there were three human rabies deaths during this five-year period.

As McKendrick points out, we should never withhold treatment due to fear of complications to rabies vaccine. In 1934 he reviewed 69,541 case histories of people who had received Pasteur treatment after being bitten by animals known to be rabid, and he found a mortality rate of 0.23 per cent in contrast to the expected mortality rate of 16 per cent in those bitten by a rabid animal without receiving treatment. Among those with complications of rabies vaccine treatment, the mortality varies from 10 per cent to 16 per cent.

2. *Types of Complications*

Horack[4] in one of the most thorough studies of rabies vaccine complications has classified the reaction into six groups, as follows:

1. Generalized urticarial rash. 2. Delayed, tuberculin type reaction at the site of injection. This is the commonest. 3. Similar to 2, but more severe with accompanying fever, headache, nausea, and generalized lympadenopathy. Such cases are prone to develop paralytic complications. 4. Simple neuritis, usually transitory, involving the cranial, especially facial, or peripheral nerves. 5. Dorsal-lumbar myelitis usually occurring in the second or third week of Pasteur treatment with a low mortality rate and complete recovery the rule. 6. Landry type of ascending paralysis with sudden onset; one-third of these cases develop bulbar paralysis resulting in death.

Bassoe and Grinker[1] reported a disseminated encephalomyelitic type distinct from the six groups mentioned above. Rarely encephalitis may occur alone. The incubation period usually varies from ten to seventeen days after initiating treatment, but it can be prolonged to four months.

In general, the more severe cases appear earlier than the mild ones.[3]

3. *Etiology*

Complications may develop in persons never bitten by a rabid animal or exposed to rabies, but

* One case that was admitted since this was written, age two years, died. It will be reported in another paper.

who have merely been given Pasteur treatment; in other words, it is evident that treatment alone can be responsible. Complications occur in either sex, and at any age, but less frequently in children and older people. The more intensive the treatment, the more likely reactions are to occur. The etiological factor is controversial,[1,3,12,13] with the type of vaccine as the focal point of discussion. Many physicians believe the reactions occur as a result of anaphylactic[11] or allergic action.[4]

According to Bassoe and Grinker[1] the pathological studies suggest that vaccinal lesions represent an attenuated rabies virus disease caused by the vaccine; toxic reactions occur in the ganglion cells without Negri bodies ever being found.

The type of vaccine used in the Pasteur treatment bears a direct relationship to the paralytic complications, according to Bassoe and Grinker, with the greatest number of accidents occurring with large doses of fresh virus; the lowest occurring with the carbolyzed virus vaccines, the usual preparation used today.[3,10] It is possible that the fixed virus is the real etiological agent, since in a few cases the fixed virus has been recovered from the spinal cord.[8]

At the Pasteur Institute it is believed that overexertion during treatment is significant in precipitating neurological complications.

4. *Review of Cases*

This series of cases with central nervous system involvement following rabies vaccine includes five different clinical entities. Encephalitis alone, encephalitis with spinal involvement as well as one with pure spinal cord manifestations are included. (See Table 1.) The number of injections of rabies vaccine ranged from 4 to 22 before onset of symptoms. All cases had daily injections as shown on the chart except case 4 who received two daily except for the first and last day, when only one was given. This case and case 3 were the only two bitten by a dog known to be rabid. In the other cases the animal was not found, so no chances were taken and prophylactic injections were given. Cases 2 and 3 were terminated because of the onset of symptoms. No reason was given as to why the physician stopped at eight injections on case 5. All cases were admitted to the Communicable Disease division after the onset of neurological symptoms following treatment given outside the hospital.

In Table 2, all cases showed spinal fluid pleocytosis with a complete lack of correlation between severity of clinical course and the maximum number of cells present. One case had a rapid onset with coma on entry to the hospital, followed by a stormy course with the maximum number of five cells, while the next most severe case in the series had a maximum number of fifteen cells on repeated spinal fluid examinations. Case 1, running a relatively mild clinical course, had the largest number of cells. Lymphocytes were the predominating cells found; the Pandy test ranged from negative to 3 plus, and it, too, was unrelated to the severity of clinical symptoms.

The symptoms in Table 3 were those usually attributed to central nervous system involvement, such as headache (five cases), stiff neck (two cases), muscle spasm, urinary retention (two cases), paraesthesias, and, in one case, difficulty in walking. Table 3 shows the main clinical findings to consist of muscle spasm of the back or neck, reflex changes, urinary retention, muscle weakness of varying degree, and vague sensory changes, the latter two usually being limited to the lower extremities. Fever usually remained under 102.5°F. with the exception of case 3 (complicated by pneumonia) and case 5, given shock therapy. These

TABLE 1.—*Times of Onset and Treatment of Complications*

Case No.	Diagnosis	No. of Injections	Day of Onset After First Injection	Age and Sex	Treatment	Result When Discharged
1.	Encephalomyelitis	21	21	17 F	Symptomatic	Improved
2.	Meningomyelitis	13	12	15 M	Prostigmine Vtamin Complex	Recovered
3.	Encephalitis	4	4	40 F	Stimulants I.V. Glucose Oxygen Sulfamerazine Prostigmine	Improved
4.	Transverse myelitis	22	12	25 M	Symptomatic	Improved
5.	Meningo-encephalitis	8	10	9 F	Typhoid "Shock" Therapy	Improved

TABLE 2.—*Spinal Fluid Findings*

Case No.	Diagnosis	Maximum Cells (Cmm.)	Maximum Protein mg. %	Pandy	Maximum Pressure in mm., Water
1.	Encephalomyelitis	230 (Lymphs Predominant)	83	2 +	240
2.	Meningomyelitis	28 (98% Lymphs)	43	Neg.	250
3.	Encephalitis	5 (Lymphs)	55	Trace	175
4.	Transverse myelitis	13 (Lymphocytes)	65	Trace	175
5.	Meningo-encephalitis	15 (Lymphocytes Predominant)	57	3 +	250

cases follow the general clinical pattern of those reported in the literature.

The treatment and course (Table 1) were mainly symptomatic, with gradual improvement. One case required treatment for urinary retention while another remained in coma four days after entry to the hospital and therefore was given typhoid vaccine shock therapy. The latter case (5) recovered following four intravenous injections of typhoid vaccine given two days apart in increasing doses of 100 million, 250, 500 and 1,000 million, respectively.

5. *Case History (Case 2)*

A 15-year-old Caucasian male was admitted to the hospital, with the chief complaints of urinary retention; numbness and tingling of the feet; difficulty in walking; a stiff back of approximately five days' duration, and a stiff neck for two days.

Four weeks previously the patient had been bitten in the right hip and left elbow by a stray dog and the wounds were cauterized about ten minutes later at the city emergency hospital. Since the dog remained undetected, the patient was given Pasteur treatment by the health department, starting two and a half weeks before entry, or ten days after the dog bite. He received 13 consecutive daily injections. Injections had been discontinued five days before entry because of the onset of the above symptoms.

The salient physical finding on admission included: temperature of 100°F. rectally; moderately severe neck and back stiffness and abdominal rigidity; paresthesias and hypesthesias from the upper abdomen (T-7) down to the mid thigh (L-2 and 3), abnormal reflexes, including absent abdominals and positive right Babinsky. There was muscle spasm in the back, neck, and hamstrings with some lumodorsal scoliosis to the left, and tenderness in the trapexius muscle which persisted for a week after entry. The patient had to be catheritized because of urinary retention for two days after admission, after which he voided voluntarily. The temperature never rose above 99°F. (oral).

The laboratory results were: The blood count, urinalysis, blood Kahn and Wasermann were negative. The bacteriological and chemical analysis of the spinal fluid was negative. The hydrodynamics of the spinal fluid were also negative with clear fluid obtained with 28 cells found per cu. mm., 98 per cent of which were lymphocytes. The Pandy test was negative.

The treatment was symptomatic, including high supplementary vitamin intake, especially of the B-complex. Fifteen mg. of prostigmine bromide was given in each of three injections in the first 48 hours to stimulate micturition.

The course in the hospital was uneventful, with gradual recovery and relief of the main symptoms and neurological signs. The patient was discharged with the diagnosis of post-rabies vaccinal meningomyelitis nine days after entry, condition improved.

6. *Discussion*

One of the conditions most commonly confused with these cases was anterior poliomyelitis which was usually an entering diagnosis to be ruled out. The onset a short time after initiating Pasteur treatment forms the main differential feature favoring the diagnosis given in the above cases. Rabies itself, sometimes feared to be present at the onset, is ruled out principally by the clinical course; also the incubation period in cases complicating rabies vaccine treatment is usually between ten and seventeen days, that of rabies three to eight weeks.

The leading pharmaceutical companies that distribute the so-called Semple type of vaccine or its modifications, dispense a carbolized killed vaccine made from rabbit inoculated brain and cord substance. Fourteen daily subcutaneous inoculations of Semple type carbolized virus vaccine is the recommended dose for the average case with two injections daily for 14 days in the more severe cases such as dog bites of the head. There are no contraindications to treatment. Luetics and alcoholics, however, should be kept under close observation.

Horak found that the more severe reactions occurred often in people with allergic history (87.5

TABLE 3.—*Clinical Features*

Case No.	Symptoms	Main Clinical Findings	Maximum Fever
1. Encephalomyelitis	Headache	Muscle spasm, neck, back, lower extremities	101°
2. Meningomyelitis	Urinary retention Paresthesia Headache Difficulty walking Spasm; back and neck muscles	Muscle spasm, neck, abdomen, back Sensory changes	100° (R)
3. Encephalitis	Fatigue Irritable Headache Feverish Pruritus Dyspnoea Backache	Coma Absent reflexes Broncho-pnuemonia	106.6°
4. Tranverse myelitis	Headache Sore, swollen arm	Muscle weakness in lower extremities with flaccid paralysis Sensory alteration (loss from upper abdomen down) Urinary retention	102.4°
5. Meningo-encephalitis	Fever Headache Sore arm	Lethargy Spasm neck muscles Signs of meningeal irritation Hyperactive reflexes	102° except with shock R 105.4° maximum

per cent), and suggested that those who have marked sensitivity or who develop it during treatment be given the benefit of desensitization. Darfman[2] advises skin testing prior to inoculation be done with horse serum.

7. *Summary*

A study of five cases of neurological complications to treatment with rabies vaccine seen at the Contagious Disease Unit of the Los Angeles County Hospital has been presented, with an analysis of the important clinical findings and their correlation to those cases previously reported.

The incidence of complications in this area is high, but not such that we are warranted in the withholding of the Pasteur treatment when indicated. However, the vaccine treatment should be given with due regard for the more severe reactions. Treatment is best suspended with the occurrence of significant neurological signs or symptoms.

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