COMPLICATIONS OF ANTIRABIC VACCINATION

Vichai Bunyasaosuk, M.D.*

Pachong Khongkha, M.D.*

The effectiveness of antirabic vaccination is well documented. According to Veeraraghavan[24] 43 per cent mortality was observed in the unvaccinated patients and 8 per cent in the vaccinated group. However antirabic vaccination should be administered according to the recommendations of the World Health Organization[28], because large number of adverse reactions was observed following the use of nerve tissue vaccine. Tangchai[22] reported 5 fatal cases of encephalomyelitis complicating antirabic inoculation in adult from this institution.

The purpose of this communication is to describe the clinical manifestations, pathogenesis and therapy of 14 patients who developed complications after antirabic vaccination in the Pediatric Department of Chulalongkorn Hospital during the period of 1966 to 1970.

Selected Case Reports

Case 1. This 14-year-old boy was bitten by a dog over the left thigh and was given antirabic vaccination at the Saovabha Institute. After the ninth injection he complained of headache and abdominal pain with occasional vomiting. After the fourteenth vaccination headache and vomiting became more pronounced, and were followed by fever and drowsiness. Physical examination at the time of admission revealed an acutely ill boy with lethargy and moderate dehydration. His oral temperature was 38.5 degree centigrade. There was no nuchal rigidity. The examination of the heart lung and abdomen was not remarkable. There was healed scar over the left thigh. Slight motor weakness of the extremities was noted. The deep tendon reflexes were within normal limits. Babinski 's sign showed flexor response. The sensation was intact. Laboratory data were as follows: hemoglobin 10 gram per cent; white blood count 14300, with 83% neutrophils and 17% lymphocytes. Blood urea nitrogen 35, Creatinine 1.2, Sodium 134, Potassium 4.7. The spinal fluid was clear with opening pressure of 190 mm. water. Pandy test was negative. There were 98 lymphocytes. Protein was 25 mg. per cent. Sugar 67 mg. per cent. It was believed that the patient had acute postvaccinal encephalitis and corticosteroid was given orally. After one week of therapy he was much improved. On the tenth hospital day he was afebrile and corticosteroid was tapered. One week later corticosteroid was reordered because of recurrence of fever. He was afebrile again after four days of therapy. He was discharged with complete recovery after four weeks of hospitalizaion.

Case 5. This 13-year-old female patient was bitten by a dog about 20 days prior to admission and was given full course of antirabic vaccination. At the

* Department of Pediatrics, Chulalongkorn Hospital, Faculty of Medicine.

end of the fourteenth injection she developed headache, fever, weakness of the legs and urinary retention. Physical examination revealed a toxic appearance girl with lethargy. Her oral temperring was 40 degree centigrade. There was right facial nerve palsy, swallowing difficulty, and dysarthria. Flaccid paralysis of both lower extremities with impaired sensation was noted. The deep tendon reflexes were absent. Rectal examination revealed poor sphincter tone.

Laboratory data were as follow: white blood count 10040, with 96 per cent neutrophils and 4 per cent lymphocytes. Urine was normal on admission but subsequently E. coli organisms were isolated. The spinal fluid was clear but pandy test was positive. There were 6 lymphocytes and 1 neutrophil. Protein was 60 mg. per cent, sugar 33 mg. per cent. Culture was negative. The patient was treated with corticosteroid and antibiotics and there was dramatic improvement. Facial palsy, swallowing difficulty and dysarthria all disappeared. Motor power and sphincter control were almost normal when she was discharged.

Case 7. This 10-year-old girl was given 14 injections of antirabic vaccine because she was bitten by a suspected rabid dog. Four days after the last vaccination she began to complain of muscular aching. The next day she developed abdominal pain and was treated by a local physician. Two days later she complained of numbness of the lower extremities, and she was unable to move her legs. Physical examination revealed a conscious and cooperative girl with normal vital signs. There was flaccid paralysis of the lower extremities with intact sensation. There was no cranial nerve palsy. The laboratory findings revealed leucocyte count of 12050 with neutrophils 67 per cent, lymphocytes 32 per cent and eosinophil 1 per cent. The spinal fluid was clear with opening pressure of 100 mm. water. Pandy test was trace. There were 282 lymphocytes and 8 neutrophils. The patient was given corticosteroid. One week after therapy she was able to move her legs. Two weeks later she could stand up and walk with support. She was discharged after four weeks of admission.

Case 8. The patient was bitten by a dog and was given antirabic vaccination. After the eighteenth injection he developed headache, diplopia and became lethargic. Physical examination revealed an acutely ill boy with high body temperature. He was stuporous and did not respond to question. His pupils were constricted. Heart and lung examinations were unremarkable. The deep tendon reflexes were within normal limits. Babinski' s sign showed flexor response. Laboratory finding revealed a leucocyte count of 9000 with neutrophils 67; lymphocytes 33. Spinal tap was traumatic. Blood urea nitrogen was 20 mg. per cent. The patient was treated with corticosteroid and antibiotics. He remained febrile and unresponsive. On the fourth hospital day he expired. Autopsy revealed marked congestion and edema of the brain with no significant lesion on cut surface. Microscopic examination showed demyelination in the paraventricular area (fourth ventricle and hypothalamus). There was perivascular cellular infiltrations. The cells were composed of lymphocytes, plasma cells and few neutrophils. Glia nodules and astrocytic proliferations were noted in the white matter.

Comment

In Thailand rabies is a major public health problem. Accurate statistics on the incidence of this disease in the whole country are not available. But at the Saovabha Institute in Bangkok over 5000 patients per year are treated with antirabic vaccine[15]. The incidence of neuroparalytic complications is 3 per 10,000. In the United States, the rate of reaction associated with nervous tissue vaccine is one in every 4000 to 8000 patients receiving antirabic treatment[23]. Greenwood[7] found an over-all incidence of one reaction to 5814 treatments on a world-wide basis in a total series of 1,297,758 patients. In the same series there were 56 fatalities equivalent to 25 per cent in those suffering neuroparalytic complications. Latimer and co-workers[11] found 40 per cent mortality in 22 cases of this complication reported in the literatures.

The duration of clinical manifestations may occur from 8 to 21 days following the first antirabic inoculation[2]. In our series the average duration is 12 days. The disease is believed to be an allergic reaction to the substances in the vaccine. No virus has been recovered from such cases nor have these syndromes been transmitted from man to animal. Rivers et al[17] produced similar pathologic lesions in monkeys by intramuscular injection of normal rabbit brain emulsions. Subsequently a number of studies have shown that experimental allergic encephalomyelitis can be induced in animals by various types of neural preparations. The used preparations varied from whole homogenates of cord or brain[5,8] to purified preparations of proteolipids,[14,27] proteins[10,20] and polypeptides[12,18,19]. Quite possibly all of these preparations are related and which endow them with the capacity to antigenically induce experimental allergic encephalomyelitis. The pathology of postvaccinal encephalitic reaction is described[1,16] as primarily one of myelin destruction, perivascular lymphocytic infiltration and microglial proliferation with little damage to the nerve cells. This is quite in contrast to the findings in known neurotropic viral disease in which there is damage to the nerve cells, with inflammatory infiltrations.

Moyer and his associates[9] and Kabat et al[13] have demonstrated that the develepement of allergic encephalomyelitis may be blocked by adrenocorticotropic hormone and by cortisone.

According to Appelbaum[2] the clinical pictures of antirabic vaccinal complications can be divided into 4 types.

1. Encephalitic type. The encephalitic type is characterized by fever, headache, pain in the body and extremities, changes in mental state and the presence of nuchal rigidity associated with positive Brudzenski and Kernig's signs, and frequently with changes in deep and superficial reflexes. The Babinski's sign is often positive.

2. Dorsolumbar myelitic type. In the dorsolumbar myelitic type, the onset is more gradual. The patient complains of back pain, followed in a few hours or days by paralysis of the legs, partial or complete anesthesia and loss of sphincter control.

3. Neuritic type. In the neuritic type, the picture is mainly one of involvement of the peripheral nerves.

4. Ascending paralysis of the landry type. This is a rare form with high fatality rate.

In some patients there may be some overlaping of the clinical manifestations.

In this series there were 7 patients with the clinical pictures of the encephalitic type and 4 patients of the dorsolumbar myelitic type. There were 3 patients who had both the encephalitic and dorsolumbar myelitic type manifestations. There was no neuritic type or ascending paralysis in our series. Vejjajiva[27] found one case of polyradiculoneuritis in his group. Lumbar punctures were performed at least once in 13 of the 14 patients. The spinal fluid was clear in most instances and frequently under somewhat increased pressure. (Table 1) A moderate increase in number of the white cells was the commonest abnormal finding. The differential count usually showed a definite predominance of lymphocytes. Spinal tap was not done in one patient (case 3) because the patient was thought to have mild degree of myelitis. Traumatic taps were observed in two patients. The results of the cerebrospinal fluid findings are shown in table 1.

Table 1. Cerebrospinal fluid findings.

patient	pressure mm. water	pandy test	no. wbc per cu.mm.	neutrophils	lymphocytes	protein	sugar
1.	190	negative	98	0	98	25	67
2.	130	negative	69	0	69	60	61
3.	–	–	–	–	–	–	–
4.	150	trace	76	5	71	50	71
5.	–	1 plus	7	1	6	60	33
6.	144	negative	24	0	24	12.5	39
7.	110	trace	290	8	291	–	–
8.	traumatic	tap					
9.	90	2 plus	270	54	216	77	60
10.	140	negative	20	0	20	25	124
11.	120	trace	87	27	60	31	77
12.	120	trace	182	2	180	–	–
13.	traumatic	tap					
14.	200	2 plus	154	0	154	–	–

In 1952 Garrison[6] reported a case of encephalomyelitis complicating antirabic inoculation in which dramatic pesponse followed cortisone therapy. Since then several reports have appeared in the literatures showing the usefulness of corticosteroid in the management of antirabic vaccine complications[3,4,21,25]. Vejjajiva[27] used corticosteroid in 30 of the 35 patients with antirabic vaccine reactions and found that 60 per cent recovered completely, 18 per cent had slight residual disability and 5 percent left disabled. The majority of those who recovered completely did so within one to two weeks. Twelve of the 14 patients in our series were given corticisteroid. Eleven patients showed dramatic response to therapy, and were discharged with complete recovery or improvement. One patient (case8) who was also treated with corticosteroid died

on the fourth hospital days, Autopsy showed postvaccinal encephalitis. Two patients who showed mild degree of myelitis were not treated with corticosteroid. Both recovered completely with symptomatic therapy.

In order to prevent serious adverse reactions following the administration of antirabic inoculation, Blatt[3] recommended that the vaccination should be stopped immediately upon the appearance of the following symptoms that were otherwise unexplained: Fever, headache, emesis, generalized weakness and weakness of the legs. Tangchai[22] noticed that all of the fatal cases of encephalomyelitis in his series received further immunization when certain neurological or systemic manifestations developed during the course of therapy. Therefore patients who are receiving antirabic treatment should be evaluated frequently by their physicians. If any symptoms or signs of adverse reactions develop, immunization must be interupted and corticosteroid should be considered.

In the United States the duck embryo vaccine has been used extensively for rabies prophylaxis since 1957. The effectiveness of duck embryo vaccine is equal to the nerve tissue vaccine when judged by frequencies of failure to prevent disease[23]. The neurologic complications associated with duck embryo vaccine have been reported in 1 of every 25,000 persons treated. Therefore the U.S. Public Health Service Advisory Committee on Immunization Practices recommends the use of duck embryo vaccine for rabies prophylaxis.

Summary

Antirabic vaccine complications were observed in 14 patients in the pediatric department of Chulalongkorn Hospital during the period of 1966 to 1970. The clinical manifestations, pathogenesis, management and prevention were discussed.

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