POSTVACCINAL ALLERGIC ENCEPHALOMYELITIS COMPLICATING ANTIRABIC INOCCULATION IN THAILAND

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Acute disseminated encephalomyelitis complicating antirabic vaccination is well known: its clinical and pathologic features are well described in respective textbooks concerning neurological disorders. At present, there is strong evidence that the pathologic lesion is an allergic reaction.(1,4,6,7,9) The relationship of this neurological damage to body reaction against foreign nervous tissue was first suspected and suggested by Von Pirquet(10) as for back as 1907. The primary pathology of the lesion is one of disseminated para-adventitial myelin destruction with relative sparing of nerve cells and axis cylinders, and non-specific white matter reaction inseparable from postvaccinial and postexanthematous encephalitis such as in smallpox and measles(4). On the other hand, the lesion is also similar to a pathologic feature produced in experimental animals by using ether-alcohal extract of animal brain tissue with or without Freud adjuvants.(6,7) During the period between 1964–1968, five fatal cases of postvaccination encephalomyelitis following antirabic inoculation were encountered among 1627 autopsies performed at the Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok. Described herein, are the clinical and pathologic main features of these five patients.

Material and Method

The formalin fixed and paraffin embedded tissue from five patients among 1627 autopsies performed between 1964–1968, at the Department of Pathology, Faculty of Medicine, Chulalongkorn University provided the basic material for this study. The staining procedures employed were the Hematoxylin and Eosin, Weil-Weigert myelin stains, and in two cases (4,5), the Seller's method for identification of Negri bodies. Viral and immunological study were also carried out in the last two cases. These last two methods excluded the diagnosis of rabies encephalitis in these cases.

Results

Case 1: (A/4637)

A 33 year old Thai man was bitten by a dog which died three days later. Antirabic vaccination

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was commenced on the following day. On the 8th day of injection, the patient developed headache but the vaccination was not interrupted. The headache became intense, and on the 13th injection day, he developed semiunconsciousness with generalized weakness of muscles. On admission, after this 13th injection, the neurological findings were dullness of mentality, marked weakness of all muscles and hyperreflexia. The white cell count was 11450 with 92 per cent neutrophils. Other laboratary findings were normal except for blood sugar, which was 174 mg. per 100 ml. The patient developed unconsiousness with fever of 41° C, at 11 hours after admission. Treatment with stercids and hypothermia was without benefit. He had profused salivation and died 8 hours later.

At autopsy the brain was 1500 gm. in weight. Multiple petichiae in temporal lobes and hypothalamus were evident. There were multiple large, dull-gray plaques involving the white matter of the cerebral cortex and disseminated small, gray-brown plaques in the white matter of the mid-brain as well as in the spinal cord. The ammon's horn, on both sides, the insula, and the posterior hypothalamus showed areas of severe hemorrhagic necrosis. Focal subarachnoid hemorrhage was observed over the base of the brain. The demyelination was found in paraadventitial regions as well as in the subependyma. The perivascular cellular infiltrate was quite heavy, composed mainly of lymphocytes and plasma cells. The adjacent brain tissue showed minute hemorrhages as well as hemorrhagic necrosis. (Fig 1) There was also a subarachnoid exudate and subarachnoid hemorrhage. Extreme vascular engorgement was noted in the subarachnoid space. The neurones displayed swelling, granularity as well as chromatolysis. Glial proliferation consis ting mainly of microglia was noted in the white matter elsewhere. (Fig. 2)

Case 2. (A/4778)

A 25 year old Chinese man was bitten by a rabid dog two weeks prior to hospitalzation. One day after being bitten, he was started on antirabic vaccine. After the sixth injection, he divelcped profuse salivation, headache, and generalized motor weakness, with difficulty in urination. Vaccination was not interrupted despite these symptoms. On the 14th day, the patient developed continuous high fever and became unconscious. At this time, patient was admitted to the hospital. The temperature on admission was 39° C and he was cyanotic. There was weakness of all limbs and deep tendon reflexes were markedly diminished. The CSF was clear, containing 7 red blood cells and one neutrophil. He died 12 hours after admission.

At autopsy, the brain weighed 1400 gms. There was marked brain edema. The white matter showed

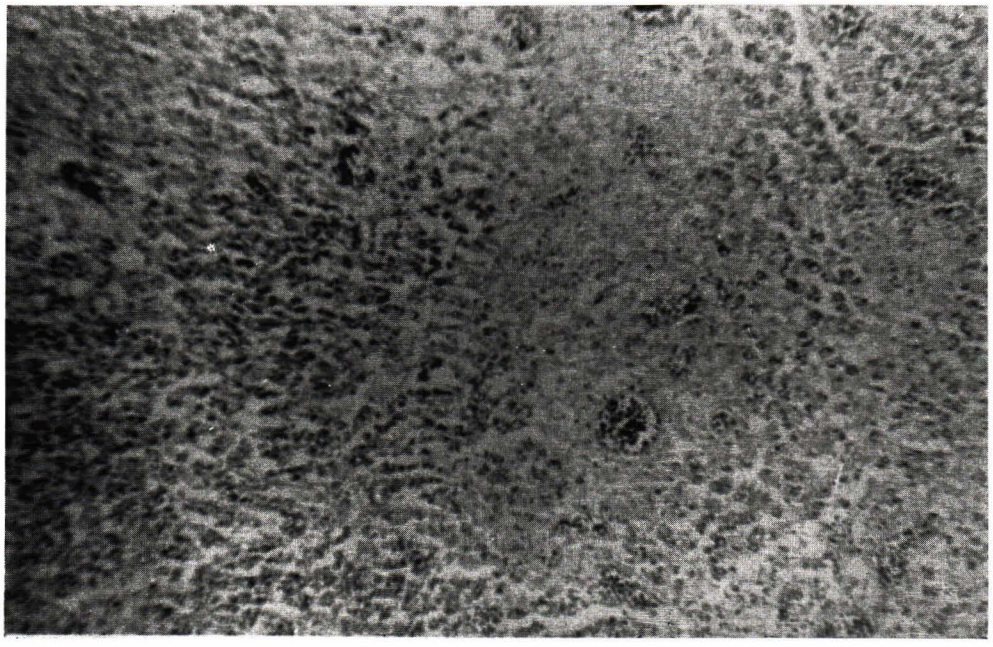

Fig 1 : Case 1 : Foci of small recent petichial hemorrhages. Note also the perivenous demyelination. Weil–Weigert Stain x 100

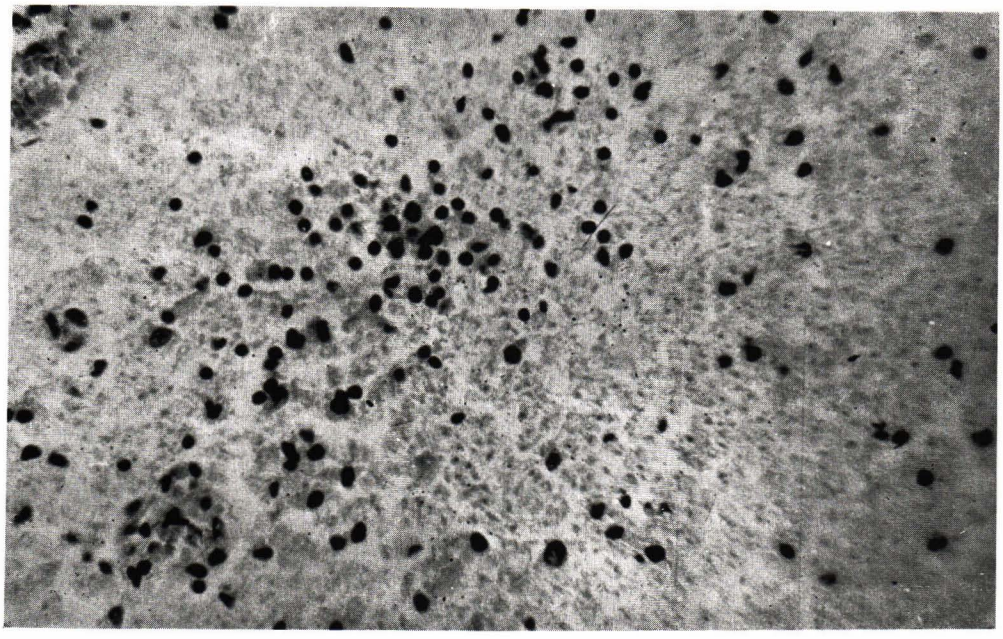

Fig. 2 : Case 1 : Glial nodules are composed of mioroglia and oligodendroglia. Perivascular glial proliferation is shown at the left lower corner of the field. H & E x 400

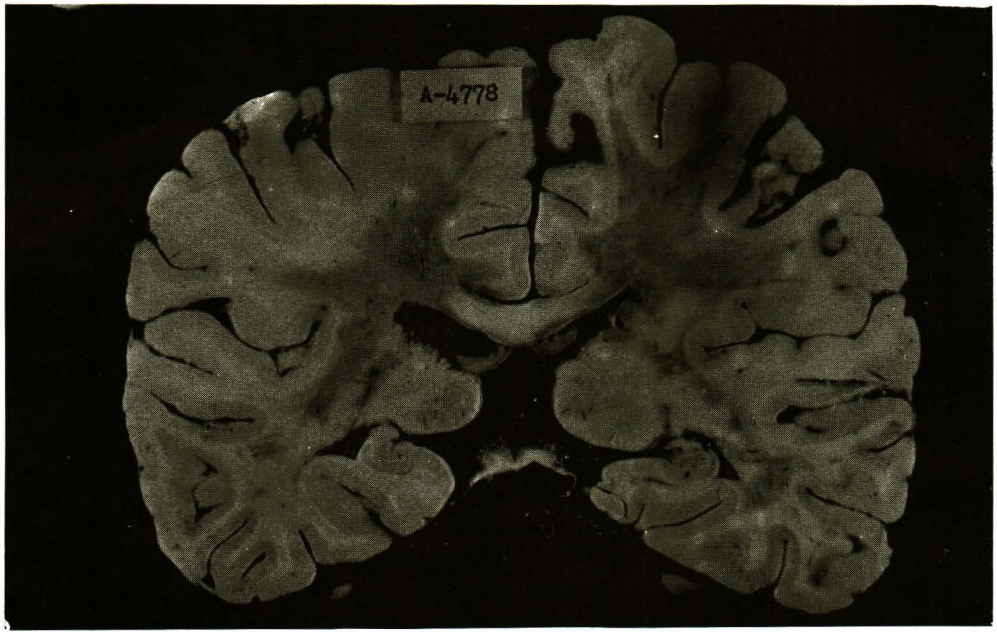

Fig. 3 : Case 2 : Large, somewhat symmetrical, dull—brownish plaques in the centrum semiovale of the cerebral hemisphere. Note small petichiae at Ammon's horn.

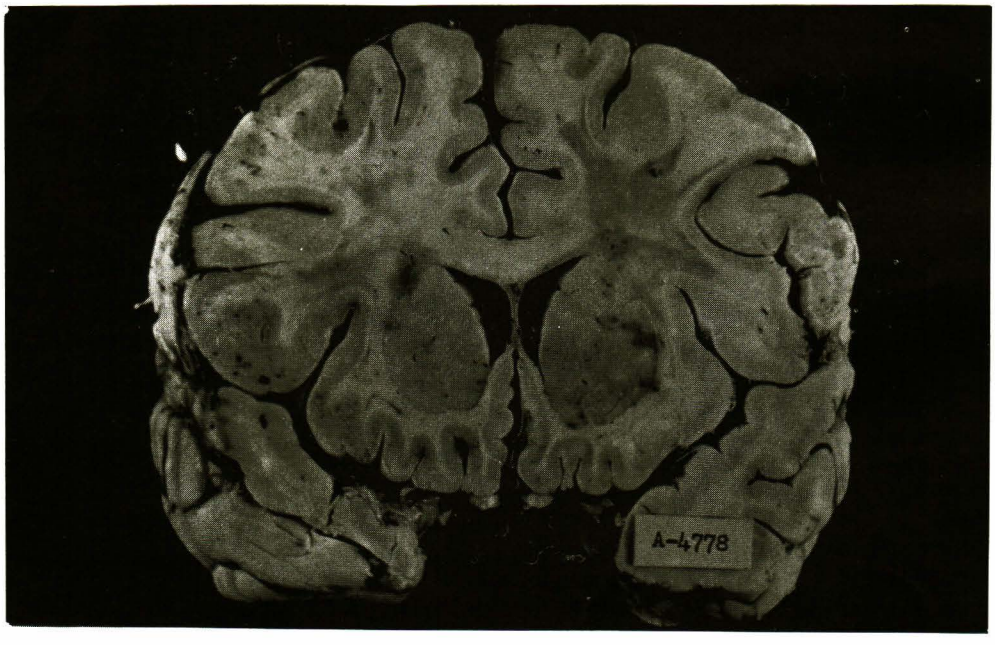

Fig. 4 : Case 2 : multiple small gray plaques as well as petichiai involving mainly the white matter, but the gray substance is not entirely spared.

symmetrical, bilateral, massive, gray–brown, dull plaques extending from the frontal lobe to the occipital lobe of the hemisphere (Fig. 3). In addition, smaller disseminated plaques were present in the mesencephalon, myelencephalon and, especially, in the white matter of the spinal cord. Foci of small petichiae were noted in the anterior white matter of the cord. (Fig. 4) Sections from the symmetrical, massive, brownish plaques reveal extensive demyelination which appears to be conglomerate from numerous subependyma and para-adventitial myelionlysis (Fig. 5) The white matter destruction, together with disseminated hemorrhagic necrosis, vascular necrosis, and neuronal degeneration are very prominent and extensive. The spinal cord showed severe and disseminated involvement, not only the parasulcus but also throughout the white matter, and grey matter was not entirely spared. The perivascular infiltration, especially of the periarteriolar and arterial regions, contained large atypical mononuclear cells as well as neutrophilic leuccytes. (Fig. 6) Some arterioles displayed necrosis of the walls and fibrin was observed around these vessels. Thrombosis, probably of platelet fibrin component, was present. (Fig. 7)

Case. 3 (A/5215)

A 27 year old Thai woman was contaminated by saliva of her own child who had been bitten by a rabid dog. For prevention, she asked for a series of antirabic vaccination. On the 9th day of injection she developed headache. On the 11th day she was unable to walk because of weakness of locomotor muscles. She received two more injections. After the last, she developed semiunconsciousness and was brought to the hospital. The Kernig's sign was positive. Bilateral pyramidal tract sign was markedly decreased. Deep tendon reflexes were absent. Nystagmus was present, both vertically and horizontally. White blood cell count was 12,500 with 87 percen neutrophils. The lumbar puncture showed a pressure of 300 millimeter of water. It was turbid, and the Pandy test was 1–2 plus. There were 785 white cells composed of 91 per cent lymphocytes. The protein was 55 mg. and sugar, 72 mg. per 100 ml. of cerebrospinal fluid. The temperature was 41° C which resisted all treatment, including hypothermia and big doses of corticosteroids.

At autopsy, the brain was edema tous, weighing 1550 grams. The white matter contained disseminated dull brownish plaques throughout, especially in the brain stem, floor of third ventricle and spinal cord. (Fig. 8) Para-adventitial areas of demyelination and perivascular exudate were most marked in the hypothala mus, mid-brain, and spinal cord. In this case, as in case 2, the perivas cular, especially periarterial and periarteriolar exudate was striking. The demyelination was also found in the subependyma of the third ventricle.

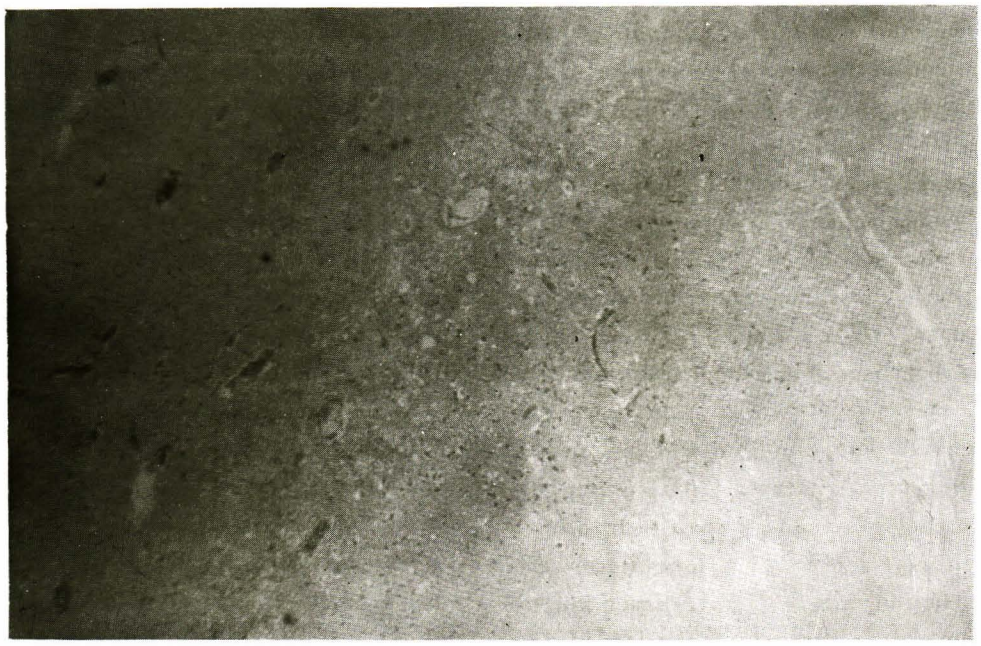

Fig. 5 : Case 2 : Massive para—ventricular demye — lination as well as multiple perivenous myelinolysis. Note congestion and thrombosis of the small vessels. Weil—Weigert x 50

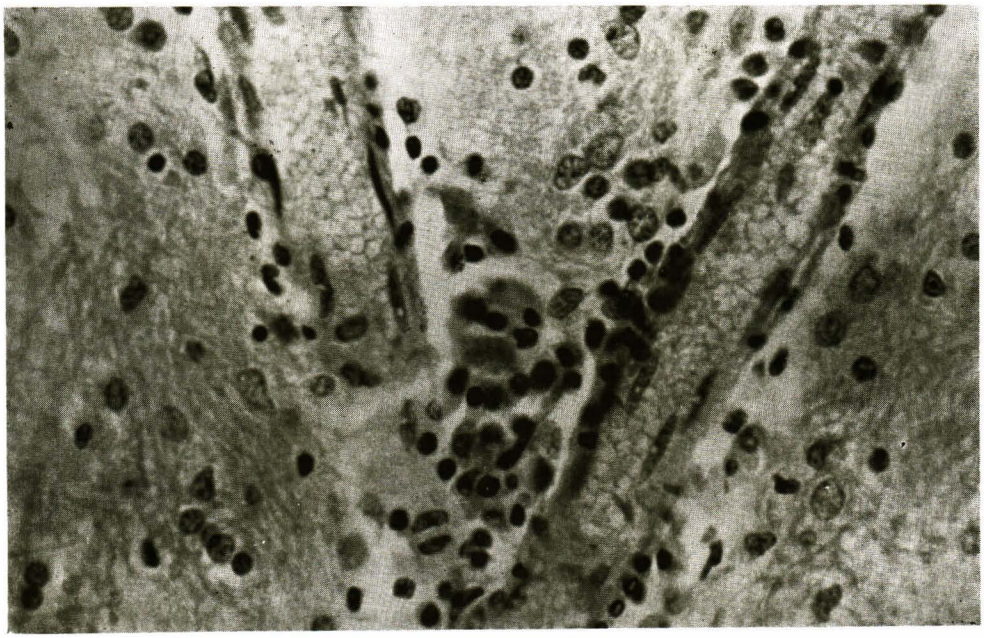

Fig. 6 : Case 2 : Periarteriolar infiltrate showing lymphocytes, large atypical mononuclear cells, and a few neutrophils. Note hyperplasis of vascular endothelium. H & E x 400.

Fig. 7 : Case 2 : Fibrin–platelet thrombus in a small arteriole in the brain H & E x 400.

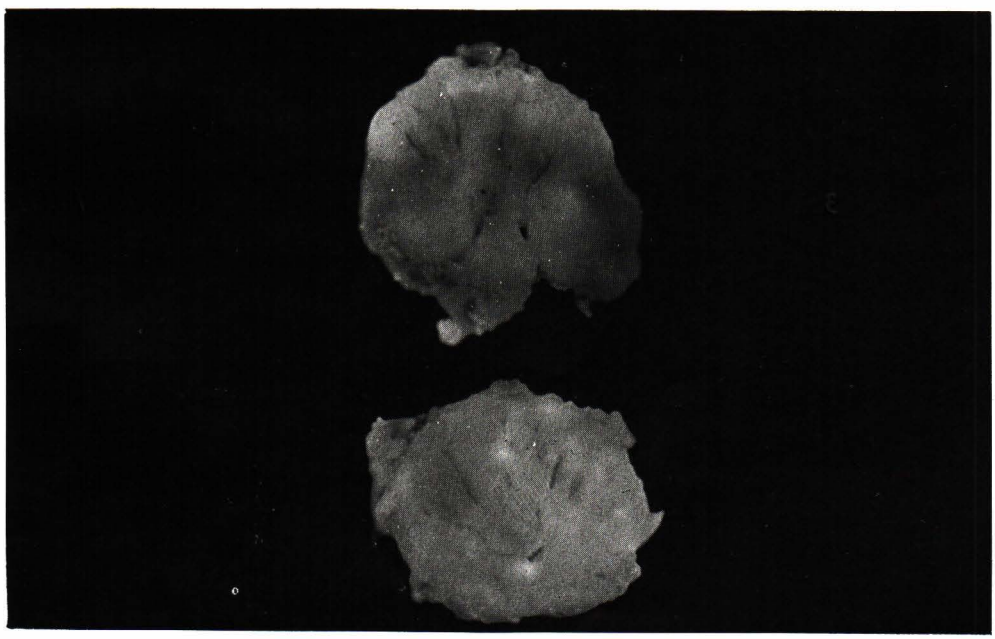

Fig. 8 : Case 3 : Multiple small, gray plaques in the spinal cord.

Foci of hemorrhagic necrosis were most marked in the paraventricular area and posterior hypothalamus. (Fig. 9) Again, marked neuronal changes were observed.

Case. 4 (A/5685)

A 43 year old Thai woman was bitten by a dog which was later proved to be infected by rabies. She received the complete 14 dose antirabic vaccination. On the very day of the last injection, she developed abdominal distress which was relieved by medication. Seven days later, she developed weakness of the lower extremities and retention of urine, and was unable to walk. The muscle power of the upper limbs was still intact, She was alert and cooperative. Flaccid paralysis of both legs was noted. The Babinski sign was negative. Hypalgesia on both limbs up to level of the second lumbar vertebra was detected Laboratory data were within normal range except for slight hyper glycemia. Steroids, 100 mg/per day were given but she died on the **3rd** hospital day.

At Autopsy the brain was 1450 grams in weight. There was marked congestion and edema. No significant lesions on the cut surface were noted on naked eye examination except congestion. There was only slight degeneration of myelin in the perivencus regions. Cellular exudate was little and consisted entirely of small mononuclear cells. In a few areas, large foamy macrophages containing light yellow granular pigment were noted. (Fig. 10) No vascular or neuronal changes were observed except for marked vascular engorgement. There was no significant neuronal degenera tion.

Case 5. (A/5701)

A 41 year old man was bitten on the left hand by a dog 2 months before admission. The dog died a day later but was not autopsied. The patient began antirabic vaccination 13 day befor admission because he felt numbness and tingling sensation at the bitten site. On the **8th** day of vaccination he developed fever but the veccination was not interrupted. On the **13th** day there was marked weakness of all muscle groups. Examination revealad nothing remarkable except for loss of motor power of extremities,left more than right, and the distal more than the proximal group. Deep tendon reflexes were entirely absent. Patient had retention of urine. He developed forced respiration and facial weakness and expired despite big doses (100 mg/day) of prednisolone which was given as soon as he was admitted.

At autopsy the brain weighed 1450 gms. There was marked vascular congestion and edema. Multiple small, ill-defined plaques were scattered throughout the white matter of the brain and cord. Numerous small hemorrhages were observed especially in the spinal cord, but no tissue necrosis was noted. Demyelination was found scattered in the para-adven-

Fig. 9 : Case 3 : An area from the hypotholamus showing severe petichial hemorrhages and hemorrhagic necrosis. H & E x 100.

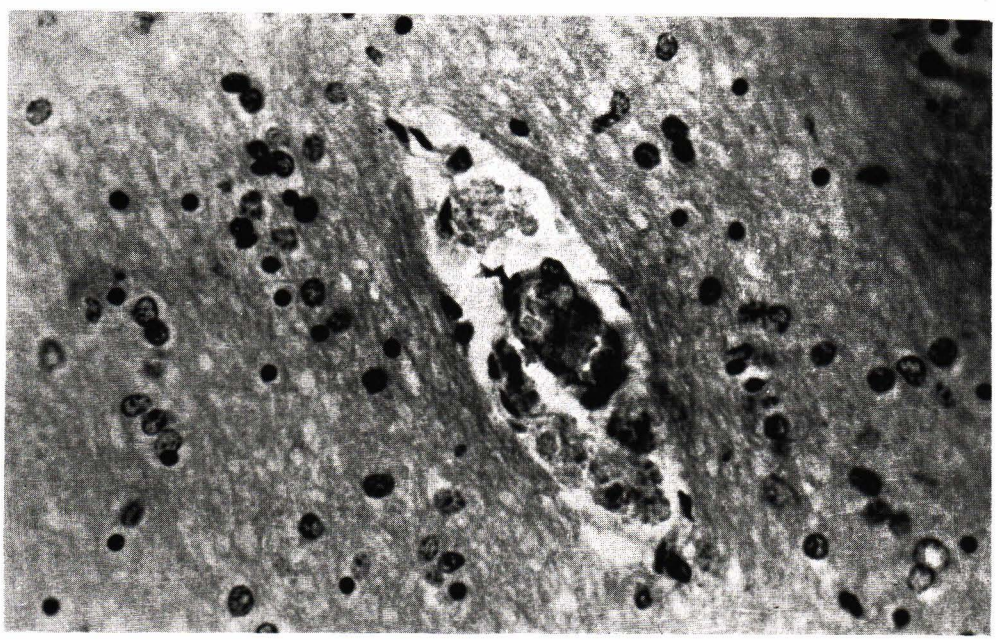

Fig. 10 : Case 4 : Perivascular infiltration is mild. Note granular pigment and vacuoles in the macrophages lying within the Virchow–Robin space. H & E x 400.

titial areas, and, especially, in the subpial regions of the spinal cord. Neuronal swelling and chromatolysis were observed in the adjacent tissue. Microglial and oligodendroglial proliferation was not striking. Perivascular infiltration was mild and the cells were lymphocytes and a few large mononuclear cells.

Comments

The antirabic vaccine which is universally employed in Thailand is the Semple vaccine. It is prepared from sheep's brain instead of of the common rabbit's brain. The virus containing brain tissue is, then, phenolized and suspended in a 1–3 percant dilution and is given to a patient in a dose of 2 ml/day, for 14 consecutive days. According ot Brain[2], the incidence of neurological complications of antirabic vaccination was between 1:1000 to 1:4000. The death rate among these patients was approximately 30 per cent. Pillai [8] found 13 patients among 279018 persons inocculated at the Coonor Research Institute, India; a ratio of 1:21463. It is difficult to obtain a definite figure in Thailand because patients suffering from fatal diseases frequently do not enter the hospital, especially in the rural areas. The duration of clinical neurological manifestation following antirabic vaccination in general has been found to be between 5–30 days, but mostly between 13–15 days[8]. It is 10–14 days according to Garrison [9], and 8–12 days according to Hurst [5]. In the present study, the average duration was 9 days.

The number of five fatal cases among 1627 consecutive autopsies is very large as compared to figures given in the textbooks. This may be explained by the fact that Chulalongkorn Hospital, where the material for this study was obtained, is under the management of the Thai Red–Cross, which also runs the Pasteur Institute in Thailand. The latter, besides being the place where vaccines are prepared and supplied, is also serving the public as an antirabic vaccination center in Bangkok.

Table I gives the summary of the main clinical and pathologic features of the cases presented. As mentioned previously, all cases were treated with big doses of corticosteroids, and in spite of that, the patients died within short periods of time, all within 72 hours after admission. The most constant symptoms in all cases were high fever which was resistant to medication and hypothermic therapy, headache, general muscular weakness and coma. Retention of urine, profuse salivation, and, occasionally, signs of meningeal involvement constitute the important features of these cases. It is interesting to note the relationship of the clinical findings of hyperthermia and profuse salivation to the inflammatory lesion in the para–ventricular region of the third ventricle and the

Table I: Clinical and Pathologic Features of Postvaccinal Allergic Encephalomyelitis after Antirabic Therapy

Case No.	Days after Vaccinath	Clinical Manifestation		Pathologic Features						
		Symptoms & Signs	Lab. Findings	Extent & distribut	Demyelination	Perivascular cuffing	Neuronal changes	Hemorrh. necrosis	Vascular changes	Glial Proliferat
1 #4637	8	Headache, Hyperthermia, Gen. muscular weakness, Salivation. Coma	Leucocytosis, Neutrophilia, Hyperglycemia	Multiple, large & Small plaques	Paraadventitial and subependyma	Moderate to Severe	Moderate	Moderate	Marked	Marked
2 #4778	6	Hyperthermia, Cyanosis, Gen. muscular weakness, Retention of urine, Profuse salivation	—	Massive &symmetrical plaques	Extensive white matter destruction	Severe with polys & atypical	Marked	Marked	Marked	—
3 #5215	9	Headache Hyperthermia, Gen. muscular weakness, Stiffneck, Nystagmus & Coma	Leucocytosis, Neutrophilia, CSF leucocytosis and Hyperglycorrhacia	Multiple small plaques	Paraadventitial and subependyma	Severe	Marked	Moderatd	Marked	—
4 #5685	14	Gen. muscular weakness, abdominal distress, Hypalgesia. Retention urine	Hyperglycemia	—	Paraadventitial	Very mild	—	—	Marked	—
5 #5701	8	Hyperthermia, Retention of urine, Resp. distress	—	Multiple & small plaques	Paraadventitial & Subpial	Mild	Moderate	Moderate	Marked	Mild

hypothalamus. It is probable that the same mechanism may explain the hyperglycemia in three of the cases. Leucocytosis and neutrophilia occurred in two instances and, since there were no other inflammatory sources found at autopsy in either case, they must be explained on the basis of the disease process intself.

Pathologically, the gross appearance of multiple dull brownish plaques was characteristic and was persent in 4 cases. Petichial hemorrhages were found in 3 cases. All brains showed extreme vascular congestion. Histologically, the demyelinating foci were found in the paraadvential areas, in the subependymal and subpial regions. They were perivenous in distribution and Adams[4] regarded this change as the most important and distinguishing feature of the disease. However, not every case of clinical encephalomyelitis which follows vaccination displays perivenous demyelination.[3] Perivascular infiltration was also prominent in almost all of the studied cases. Both the venous and the arterial vessels were involved, which is not usually the case in infective encephalitis, in which the cellular infiltrate is found mostly around the venous blood vessels. The cells were lymphocytes, plasma cells and, in some instances, a few neutrophils. The infiltration was enormous in cases 1 and 2, as compared to an almost entire absence in case 4. Pigment laden macrophages and foam cells were noted in one case (case 4). Clinical meningitis with subarachnoid infiltration was also observed in two cases, (cases 1, 3). Gliosis was not prominent and was composed mainly of microglia and oligodendroglia.

The nerve cells, in all cases except case 4, displayed definite changes, especially in the hypothalamus, midbrain, and the spinal cord. In general, the cells were markedly swollen and pale and many showed central chromatolysis and vacuolation. This is identical with changes observed in generalized anoxic degeneration. The absence of accompanying granular degeneration of the cerebellum as well as the association of neuronal changes to areas of severe affection appear to be evidence against anoxic origin in these cases. The involvement of the brain stem, the hypothalamus, and the spinal cord together in all cases, may be important and characteristic features of the fatal cases of postvaccination allergic[1] encephalomyelitis in this study.

Severe demyelination with massive bilateral symmetrical, dull brownish plaques, seen grossly in case 2, is seldom encountered in postvaccinal encephalitis. The lesion is similar to schilder's sclerosis microscopically.

The disease is believed to be a hypersensitivity reaction, although some authorities, notably Hurst[5], voiced strong disagreement to this

Hurst[5] concluded from experimental work that there were many ways in which demyelination could be produced, such as anoxia, infection, and various noxious stimuli. However, the similarity of this disorder to experimental allergic encephalitis and the prevention and abolishment of the clinical symptoms and signs by cortisone strongly favor allergic etiology. Reports on attempts to differentiate between lesions among those primarily allergic demyelinating conditions which are sometimes known as perivenous encephalomyelitis by morphology alone, have been published in Europe.[3]

In this study, almost all of the patients developed certain neurological or systemic manifestations during the course of therapy, yet in none of these cases was the process of vaccination interrupted. The subsequent administration of the vaccine after the damage had already begun undoubtedly played the most important role in the production of irreversible lesion and death of the patients. Antirabic vaccinations in the provincial areas in Thiland are fequently given by nonphysician health officers who do not have sufficient training in symptomatology of diseases. They, naturally, are unable to recognise the seriousness of the symptoms or they may interpret them as features of rabies itself. From this study, it is clearly shown that cases of allergic postvaccinal encephalitis following antirabic inocculation are not rare and might even be found to be much more common than expected if all cases were reported to the hospitals. Therefore, special measures must be carried out in order to prevent the occurrence of this malady. If physicians are not available in the remote areas, the health officers must be well informed and specially trained in the recognition of various reactions which may occur following mass therapy or preventive measures of any form. By the same token the validity of the use of Semple vaccine prepered from sheep brain must be carefully reappraised and reconsidered.

Summary

During the period between 1964–1968, five fatal cases of postvaccinal allergic encephalomyelitis following antirabic inocculabic among 1627 consecutive autopsies were recorded. The clinical and pathologic features of individual case were presented.

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References

1. Adams, R.D. and Kubik, C.S. : The Morbid Anatomy of the Demyelinative diseases. Am. J. Med. 12 : 510; 1952.

2. Brain, L. ; Diseases of the Nervous System, sixth edition, Oxford University Press, London, 1968 pp. 436.

3. De Vries, E. : Encephalitis following Vaccination and Exanthematous Diseases ; Proceedings of a Symposium on the Neruopathology, Electroencephalography and Biochemistry of Encephalitides, Elsevier Publishing Company, Amsterdam, 1961 pp. 96–99.

4. Garrison, S.C. : Encephalomyelitis Complicating Antirabies Vaccination Treated with Cortisone. Am. J. Med. 12 : 135; 1952.

5. Hurst, W.E. : Experimental demyelination in relation to human and animal diseases. Am. J. Med. 12 : 547; 1952.

6. Kabat, E.A., Wolf, A. and Bezer, A. E. : The rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants; J. Exper. Med. 85 : 117 ; 1947.

7. Olitsky, P.K. and Yeger, R.H. : Acute Disseminated Encephalomyelitis produced in Albino Mice, Proc. Soc. Exp. Biol. & Med. 70 : 600; 1933.

8. Pillai, T.D.C. : Neuroparalytic Accident following Antirabic inoculation. J. Indian Med. Ass. 41 : 507; 1963.

9. Rivers, T.M., Sprunt, D.H. and Berry, G.P. : Observation on attempts to produce acute disseminated encephalomyelitis in monkeys. J. Exp. Med. 58 : 39; 1933.

10. Von Pirquet, C. quoted by Hurst, E.W. in Am. J. Med. 12 : 547; 1952.