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Human rabies encephalomyelitis

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Summary

Seven weeks after he was bitten on the lip by a puppy in the Gambia a patient showed symptoms of rabies. Passive and active immunisation was begun three days after the onset of symptoms. The evidence indicated that death was a direct consequence of the central nervous system disease rather than any associated complication. Our inability to alter the course of the illness appreciably emphasises the importance of immediate postexposure immunisation in rabies and draws attention to the present lack of effective means of preventing virus replication within the central nervous system.

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Introduction

Human rabies has been regarded as a rapidly fatal disease, but recently two patients who were vaccinated before the onset of symptoms have recovered,^{1,2} and there have been reports of prolonged survival in others not vaccinated but treated intensively.³⁻⁵ Optimal intensive care might reduce mortality,^{1,4} but our experience, reported here, suggests that in a previously unvaccinated patient death occurs from direct nervous system damage and not from recognised complications. This conclusion may have implications for environmental health in the United Kingdom as rabies spreads westwards.

Case report

A 37-year-old man was bitten on the lip by a stray puppy in the Gambia on 14 April 1975. No further action was taken and nothing certain about the animal is known. Fifty-one days later the patient developed tingling on the inner aspect of the left arm, which by the next day had spread to affect the whole arm and to a lesser extent the other limbs. He also had difficulty in swallowing fluids but could eat food. On the third day his wife ran him a bath, but he became agitated and was unable to wash. On admission to the Royal Hospital, Banjul, he was agitated and continuously spitting saliva into a towel. Examination showed nothing abnormal except absent tendon reflexes. He asked

for a drink but when this was brought he suddenly leapt to his feet and rushed to the window uttering a strangled cry. The referring physician saw this episode, questioned the patient about previous bites, and diagnosed rabies. Chlorpromazine and intravenous fluids were given followed by duck embryo vaccine and 4000 IU of horse antirabies serum subcutaneously before he was transferred to London by aircraft.

On arrival on the sixth day of the illness (all day values date from the onset of symptoms) he was lucid and orientated and gave a clear account of the circumstances of the bite, but he was agitated, apprehensive, and continuously spitting saliva. He was gripped at intervals by powerful step-like inspiratory spasms of an apneustic type which interfered with respiration and speech. Cyanosis was present at the end of the spasm and his speech would progressively rise in pitch.

Intravenous diazepam was used initially but he rapidly became confused, struggling violently, and the spasms continued. Further sedation with diazepam and phenobarbitone, paralysis with pancuronium, and artificial ventilation were instituted. After urinary catheterisation and insertion of a central venous line tracheostomy was performed. Heparin 1000 IU was given subcutaneously twice a day.

A 17-day course of duck embryo vaccine was begun on day 5. Two units of human antirabies serum were given on day 9 and one on day 10, totalling 15 000 IU (200 IU/kg).

NEUROLOGICAL COURSE

From day 7 cerebral function was assessed by electroencephalography (EEG; 8 channel parasagittal montage) rather than clinically because of sedation and paralysis. On days 7-10 there was a dominant 10 cycle/s activity with no response to pain or passive eye opening. After a brief withdrawal of sedation and neuromuscular blockade to aid assessment on day 10 there was a return of spontaneous spasms and profuse production of saliva and cardiac dysrhythmia but no return of consciousness. On day 14 repeat withdrawal of medication showed no spontaneous movement or muscle response to nerve stimulation. No further sedation or pancuronium was given. The EEG now showed dominant 6 cycle/s activity, which tended to occur in bursts, and slower frequencies, which indicated deterioration in cerebral function. Amplitudes progressively declined and by day 20 there was no EEG evidence of cerebral activity.

Motor nerve conduction was blocked from day 14, and sensory nerve conduction studies in an upper limb (day 20) showed an absence of afferent volleys.

Cerebrospinal fluid indices, normal on day 10, were abnormal by the 17th day (protein 1.75 g/l; cells 80/ μ l; pressure 250 mm H₂O), when mild papilloedema was noted. The latter resolved in two days with dexamethasone and mannitol but by day 29 the CSF protein had risen to 35 g/l with 312 cells/ μ l.

At day 34 cerebral activity in the EEG and reflex activity were still absent and the patient could not maintain spontaneous respiration. Life support measures were withdrawn.

CARDIOVASCULAR COMPLICATIONS

A transient episode of hypotension (systolic pressure 60 mm Hg) on the seventh day responded to intravenous fluid. Electrocardiography showed a sinus tachycardia (150 beats/min) interspersed with runs of nodal rhythm that were increased by stimulation of the trachea or were associated with spontaneous spasms. Propranolol and atropine successfully treated the dysrhythmias.

On day 17, after a diuresis caused by mannitol given for papilloedema, an episode of 2:1 atrioventricular block appeared and was treated with an isoprenaline infusion (2 μ g/min) which was safely tailed off after 12 hours. On day 27 a spontaneous bradycardia occurred with bizarre ventricular ectopics, but sinus rhythm was rapidly restored with adrenaline and defibrillation.

In the last week of life an isoprenaline infusion was needed to maintain an adequate blood pressure.

ELECTROLYTE AND METABOLIC COMPLICATIONS

Factors complicating fluid balance were diabetes insipidus, paralytic ileus (present throughout), intermittent pyrexia, and the need for parenteral feeding. On admission dehydration and hypokalaemia were corrected by intravenous replacement. On day 11 transient oliguria,

unassociated with changes in pulse or blood pressure, responded to frusemide. Renal function subsequently remained normal.

Throughout the illness the patient was mildly hypernatraemic and on day 14 produced seven litres of urine. Neither hyperglycaemia nor the mild uraemia induced by intravenous feeding was confirmed as the cause and diabetes insipidus was diagnosed (plasma osmolality 315 mmol/l (mosmol/l), urine 130 mmol/l). This was managed by intramuscular vasopressin in oil 2 IU every 48 hours.

RESPIRATORY COMPLICATIONS

From the day of admission a Pao₂ of 9.3-13.3 kPa (70-100 mm Hg) and a Paco₂ of 4.0-5.3 kPa (30-40 H mmHg) were maintained by forced ventilation with air or, during two episodes of pneumonia, oxygen-enriched (30%) air. Chest infections were treated with ampicillin.

LABORATORY INVESTIGATIONS

A progressive normochromic normocytic anaemia required correction by transfusion on day 29. The white cell count, initially 20×10^9 /l (20 000/mm³), fell progressively to 6×10^9 /l (6000/mm³), while the erythrocyte sedimentation rate rose from 1 mm in one hour to over 150 mm in one hour.

The serum bilirubin concentration fell quickly from 34 μ mol/l (2.0 mg/100 ml) to normal but the serum aspartate aminotransferase remained raised at 30 IU/l.

VIROLOGICAL STUDIES

Changes in serum antibodies, measured by the indirect fluorescent antibody technique and negative until day 12, are shown in the figure.

Rabies antibody levels in patient's serum (●) and CSF (○). — = Mouse neutralising antibody. - - - = Indirect fluorescent antibody.

Neutralising antibody titres were obtained by cerebral inoculation of mice and international units (not shown in figure) calculated by reference to standard sera. They were 1/22 (0.5 IU/ml) on day 7, 48 hours after receiving horse antirabies serum (the method does not distinguish between horse and human antibody) and 1/125 (3.3 IU/ml) on day 10 after receiving human antiserum, falling until day 18 and subsequently rising again to 1/3715 (83 IU/ml) on day 33.

Antibodies appeared later in the CSF than in serum. Neutralising antibodies reached a titre of 1/22 (0.5 IU/ml) on day 21 and indirect fluorescent antibody titres reached 1/2560 by day 29, long after cessation of cerebral activity.

It proved impossible to isolate the virus by mouse inoculation techniques from either saliva, CSF, or corneal smears sampled throughout the illness. Mouse intracerebral inoculation, Sellar's test for Negri bodies, and staining for rabbit antigen by immunofluorescence were negative in necropsy studies on cerebral cortex,

spinal cord, posterior root ganglion, sciatic nerve, and cardiac muscle. Electron microscopy of the last two tissues failed to show the virus.

MORBID ANATOMY

Necropsy was performed two hours after death. Both lungs showed zones of collapse without secondary infection. The heart was enlarged with a greatly thickened left ventricle. There was no evidence of myocarditis. The liver and kidneys were slightly enlarged and the spleen was five times its normal weight.

Brain and spinal cord were diffusely softened and the spinal subarachnoid space was distended by purulent exudate. Histological examination failed to show any intact neurones in the central nervous system. Peripheral nerves displayed widespread axonal degeneration with loss of myelinated and unmyelinated fibres together with a heavy mononuclear infiltrate throughout the nerve and occasional multinucleate giant cells. Dorsal root ganglia showed similar changes.

Discussion

There can be no doubt about the diagnosis in this case despite our failure to isolate the virus. The history, the characteristic hydrophobia, and the great rise in antibody titres are consistent with findings in other cases of rabies,³⁻⁵ and the titres were well above those seen with vaccination alone. Antibodies were also present in CSF. Vaccination began only after the appearance of clinical signs so vaccinal rabies encephalomyelitis can be excluded.

It is well recognised that virus cannot be isolated from either animals⁶⁻⁷ or men³⁻⁵ who have survived with the disease for long periods. This process of "autosterilisation" presumably accounts for the failure to isolate virus in the two reported cases of recovery from rabies¹⁻² and in our case.

The problems of management, which were similar to those in other reported cases, concerned many systems. It has been suggested^{1-3,4} that successful management of these problems might lead to recovery without prior vaccination. Unfortunately our case provides no support for this view, for the reasons set out below.

In one patient with rabies who received intensive care³ cardiovascular problems were prominent and were the eventual cause of death. Our patient suffered only two episodes of hypotension, on days 7 and 27. The first, resulting from our failure to take account of salivary losses of 2 litres a day, was corrected within 30 minutes by fluid administration; and the second, associated with a severe bradycardia, lasted less than three minutes. These episodes seem unlikely to have contributed to the neurological deficit as the EEG was normal for some days after the first episode and had shown no cerebral activity for a week before the second. At no stage was there circulatory arrest, nor was there any necropsy evidence of myocarditis.⁸ Dysrhythmias were easily controlled with atropine and propranolol and unlike other cases³ there were no major thrombotic episodes, possibly owing to the use of low-dose heparin.

Abnormal lung function has been described in rabies^{1,3} and a specific rabies pneumonitis has been postulated, though this has not been universally accepted.⁹ Our patient showed only chest infection with consolidation (a common complication or artificial ventilation) and maintaining adequate blood gases was not difficult.

Renal function remained excellent throughout. Extrarenal fluid and electrolyte problems were prominent but correctable.

Nevertheless, despite the successful management of complications, there was progressive damage to the nervous system. The typical early features of paraesthesiae, anxiety, irritability, and restlessness, accompanied on day 3 by absence of tendon reflexes, which possibly indicated early peripheral nerve damage, gave way to hydrophobia and muscle spasms on day 5. The patient was lucid on day 6 but was unresponsive to painful stimuli four days later. The EEG began deteriorating on the 10th day and progressively declined, showing no cerebral activity by day 20. Damage to peripheral nerves seemed to parallel that of the central nervous system. There were spontaneous movements on day 10 but from day 14 the nerves were inexcitable.

Mild papilloedema and a slight increase in CSF pressure as seen on day 17 has been described by others,^{3,4} but this was unlikely to have contributed greatly to the neurological deficit in our case which, on the EEG evidence, was already well advanced.

The progressive and total destruction of the nervous system, suspected clinically, was confirmed at necropsy. Although autolysis after brain death¹⁰ might have accounted for some changes, it could not have accounted for the total loss of neurones in brain and spinal cord that was associated with Wallerian degeneration in peripheral nerves, loss of dorsal root ganglia, and extensive mononuclear infiltration.

Other patients who have survived for long periods have shown similar changes,^{3-5,7} as has one patient who died after exposure to a "fixed" strain of virus and who was not ventilated.¹¹ Dupont and Earle,¹² reviewing 49 cases of rabies, were unimpressed by degenerative changes in nerve cells, but their patients died on average 7.4 days after the onset of symptoms. Prolonged survival seems to allow extensive changes to occur. The paralytic form of rabies has been recognised for many years.¹³⁻¹⁵ The findings in the spinal cord and dorsal root ganglia were similar to those in other reports^{13,16} and presumably account for the deterioration in peripheral nerve function.

Our case illustrates the inadequacy of current therapeutic measures in rabies and the need to emphasise prophylactic immunisation and environmental health measures. The regimen of active immunisation recommended by the World Health Organisation given before the onset of symptoms does reduce mortality.¹⁷ Hattwick *et al.*¹⁸ have suggested that post-exposure treatment should include 15-50 IU/kg of human immune plasma and a 23-day course of duck embryo vaccination. In our case 200 IU/kg of plasma and vaccination proved ineffective. Possibly higher serum or CSF levels of antibody are needed to protect, or antiviral agents may be useful. Cytarabine (arabinsyl cytosine) unexpectedly reduced rabies virus yield in cell cultures,¹⁹ and in animals methods aimed at stimulating endogenous interferon confer protection against the rabies virus.^{20,21}

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References

- Hattwick, M A W, *et al*, *Annals of Internal Medicine*, 1972, **76**, 931.
- Rabies Surveillance for the Americas, December, 1972, 90.
- Bhatt, D R, *et al*, *American Journal of Diseases of Children*, 1974, **127**, 862.
- Rubin, R H, *et al*, *Journal of Infectious Diseases*, 1970, **122**, 318.
- Emmons, R W, *et al*, *Intervirology*, 1973, **1**, 60.
- Bolin, V S, *Journal of the American Veterinary Medicine Association*, 1959, **134**, 90.
- Lodmell, D L, *et al*, *Journal of Infectious Diseases*, 1969, **119**, 569.
- Cheetham, H D, *et al*, *Lancet*, 1970, **1**, 921.
- Janners, S, *Annals of Internal Medicine*, 1972, **77**, 660.
- Walker, A E, Diamond, E L, and Moseley, J, *Journal of Neuropathology and Experimental Neurology*, 1975, **34**, 295.
- Winkler, W G, *et al*, *Journal of the American Medical Association*, 1973, **226**, 1219.
- Dupont, J R, and Earle, K M, *Neurology (Minneapolis)*, 1965, **15**, 1023.
- Knutti, R E, *Journal of the American Medical Association*, 1929, **93**, 754.
- Hurst, E W, and Pawan, J L, *Journal of Pathology and Bacteriology*, 1932, **35**, 301.
- Love, S V, *Journal of Pediatrics*, 1944, **24**, 312.
- Banerjee, A K, and Chopra, J S, *Neurology (Bombay)*, 1974, **22**, 83.
- Habel, K, and Koprowski, H, *Bulletin of the World Health Organisation*, 1955, **13**, 773.
- Hattwick, M A W, *et al*, *Journal of the American Medical Association*, 1974, **227**, 407.
- World Health Organisation Expert committee on Rabies, *Sixth Report*. Technical Report Series, No 523, p 5. Geneva, WHO, 1973.
- Fenje, P, and Postic, B, *Nature*, 1970, **226**, 171.
- Emmons, R W, and Postic, B, *Journal of Infectious Diseases*, 1971, **123**, 426.