Comment

The ability of this patient's serum to bind complement to red cells at physiological temperatures is consistent with the clinical picture of severe haemolysis. Although agglutination was not demonstrable above 32°C IgM molecules were presumably bound in sufficient numbers to initiate efficient complement activation even at 37°C. The results of the absorption experiment clearly show independent specificities for the cold agglutinin and the mycoplasma antibody, and are therefore at variance with the suggestion that these cold agglutinins are cross-reacting mycoplasma antibodies.[2 3]

We thank Dr Hillas Smith for permission to report on one of his patients.

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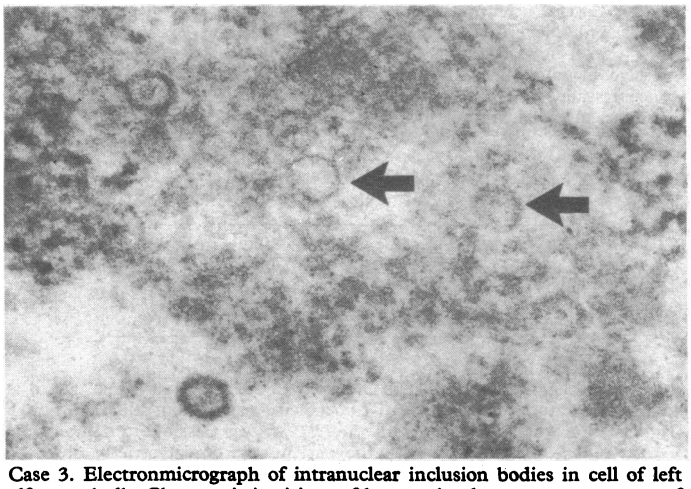
Transolfactory spread of virus in herpes simplex encephalitis

Unlike most encephalitides, acute necrotising encephalitis caused by *Herpesvirus hominis* type I exhibits several unique features, including a tendency to affect the limbic system, often asymmetrically and resulting in maximal damage to one or other temporal lobe. In a recent case[1] herpesvirus was especially prevalent throughout the limbic system and in the necrotic olfactory bulbs, suggesting that transolfactory spread of virus may be important in pathogenesis. The next three cases were therefore similarly investigated.

Case reports

Case 1—A 78-year-old man was admitted in coma after three days of rapidly progressive confusion and drowsiness. Examination showed neck stiffness, fever, and hypertension. The cerebrospinal fluid contained 25×10^9 red cells/l (25 000/mm^3) and 82×10^6 white cells/l (82/mm^3) (48% lymphocytes); normal glucose and protein concentrations; and negative Gram and Ziehl-Neelsen. He developed prolonged seizures, deteriorated, and died after five days.

Case 2—A 66-year-old woman was admitted in coma after three weeks of gradually progressive dementia, right-sided weakness, and convulsions.



Case 3. Electronmicrograph of intranuclear inclusion bodies in cell of left olfactory bulb. Characteristic virions of herpes simplex are present, some of which (arrowed) show unusual swelling, loss of nucleic acid core, and partial fragmentation of thin nucleocapsids, presumably resulting from adenine arabinoside. ×26 000 (original magnification).

Neck stiffness, right hemiplegia, and fever were present. CT brain scan was normal, and bilateral carotid angiograms showed brain swelling. Cerebrospinal fluid contained 40×10^6 white cells/l (80% lymphocytes) and 2·8 g protein/l; Gram and Ziehl-Neelsen stains, culture, and complement fixation tests for herpes, mumps, and measles viruses gave negative results. She died four days after admission.

Case 3—A 2½-year-old girl was admitted after a "febrile convulsion." She presented with pharyngitis, otitis media, fever, and a 12-hour history of left-sided facial twitching. The electroencephalogram and CT brain scan suggested encephalitis. Cerebrospinal fluid was normal. Viral studies, which included complement fixation tests on serum and cerebrospinal fluid, and culture of cerebrospinal fluid, throat, and rectal swabs gave negative results. Adenine arabinoside was started on the third day but she continued to deteriorate and died on the seventh day.

In each of these cases the brain showed all the features characteristic of acute necrotising encephalitis, including unilateral swelling and necrosis of the temporal lobe, panencephalitis without inclusion bodies, and abundant herpes simplex virus on electron microscopy. Herpes simplex virus was especially prevalent in the left and right temporal lobes and throughout the limbic system in cases 1 and 2, but in case 3 the virus was more evenly distributed throughout both hemispheres. Interestingly herpes simplex virus was found in the necrotic olfactory bulbs (figure). Necrotic cells containing herpes simplex virus were found in both right and left bulbs in each case and were associated with pronounced degeneration of myelinated fibres and prominent astrocytosis and gliosis in the olfactory tracts.

Comment

The route by which herpes simplex virus enters the brain in acute necrotising encephalitis is unknown. Haematogenous spread is the usual explanation, though in most cases no primary focus is found outside the nervous system. After the isolation of latent herpes simplex virus in various sensory ganglions,[2 3] a theory was formulated whereby virus supposedly reaches the floor of the cranial fossae via tentorial branches from the trigeminal ganglia.[4] My findings, however, would implicate a more direct route. The presence of herpes simplex virus in the necrotic olfactory bulbs, the degeneration in the olfactory tracts, and the distribution of the virus within the rhinencephalic areas suggest that the olfactory apparatus is the principal pathway in the pathogenesis of acute necrotising encephalitis in man.

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Acute haemolysis and renal failure after nomifensine overdosage

Nomifensine is an antidepressant unrelated to the tricyclic or tetracyclic drugs. No serious toxicity has been reported after overdosage,[1-3] but we report a case of acute haemolysis and renal failure requiring haemodialysis in a patient with nomifensine poisoning.

Case report

The patient, a previously well 25-year-old woman was admitted two hours after allegedly taking nomifensine 2 g (80 capsules), nitrazepam 100 mg, and chlordiazepoxide 300 mg. She had been prescribed nomifensine six months before and had taken it regularly for three months and then intermittently. On admission she was unconscious although responding to stimulation, her blood pressure was 110/70 mm Hg, and her pulse was regular at 120/min. She regained consciousness after six hours but remained drowsy. Two days later she complained of bilateral loin pain and was noted to be pale and oliguric. Her plasma and urine were the colour of creosote and there was evidence of acute intravascular haemolysis. Her plasma haemoglobin concentration

was 0·94 g/l, haptoglobins 0·12 g/l, and lactate dehydrogenase 1664 U/l. A methaemalbumin test was positive. Her haemoglobin concentration was 10·8 g/dl but subsequently fell to 5·3 g/dl. Her plasma bilirubin concentration was 26 μmol/l, (1·56 mg/100 ml), but other liver function tests remained normal and methaemoglobin was not detected. The direct Coombs test was positive with an anti-IgG antibody titre of 1 in over 800. A weak autoantibody without rhesus or other major blood group specificity was found in her serum by the automated enzyme technique of Marsh.[4] Red cell glucose-6-phosphatase dehydrogenase activity and haemoglobin electrophoresis were normal.

Her platelet count fell to 46×10^9/l (46 000/mm^3) on the third day, but there was no other evidence of definite disseminated intravascular coagulation. Immunoglobin and complement concentrations were normal and the result of an autoantibody screen including antinuclear factor was negative. The presence of nomifensine in her plasma and urine was confirmed by gas liquid chromatography. No other drugs were detected on screening the urine. Her plasma urea and creatinine concentrations rose from 3·0 mmol/l (18 mg/100 ml) and 99 μmol/l (1·1 mg/100 ml) respectively on admission to 45 mmol/l (270 mg/100 ml) and 1045 μmol/l (11·9 mg/100 ml) four days later. Urine tests for protein, haemoglobin, and urobilinogen were strongly positive. She became anuric and haemodialysis was required on six occasions before the diuretic phase began 10 days later. A renal biopsy specimen obtained 10 days after admission showed acute tubular necrosis with no evidence of disseminated intravascular coagulation. At this time the Coombs test had become negative and the platelet count had returned to normal. Improvement was maintained and she was discharged home one month after taking the nomifensine. Two months later her haemoglobin, platelet count, and plasma urea and creatinine concentrations were all normal. Twenty months after the overdose she remained well with a haemoglobin concentration of 14·5 g/dl and a normal blood film.

Comment

Acute haemolysis and tubular necrosis occurred in this patient after overdosage of nomifensine and possibly nitrazepam and chlordiazepoxide. In our experience of many thousands of cases of benzodiazepine poisoning we have never encountered these complications, and we are unaware of any such reports. There is much less experience of nomifensine overdosage, but in 28 reported cases there was no serious toxicity[1-3] and haemolysis was not encountered in preclinical toxicity studies in animals (P Stonier, personal communication). Bournerias and Habibi,[5] however, described immune haemolytic anaemia and impaired renal function in a patient taking therapeutic doses of nomifensine intermittently. Our case is very similar and there was no other obvious cause for haemolysis. Unlike these investigators, we were unable to demonstrate nomifensine-dependent agglutination of red cells in response to the antibody and, unfortunately, studies with red cell eluates were not carried out. The low serum antibody titre with a strongly positive Coombs test in our patient suggests that the antibody was of high affinity and strongly bound to erythrocytes. Probably she developed autoantibodies to red cells while taking nomifensine intermittently and subsequently suffered massive haemolysis after an overdosage. Although serious, such reactions to nomifensine seem to be very uncommon.

We thank Dr S H Davies, Department of Haematology, Royal Infirmary, Edinburgh, and Dr P Stonier (Hoechst UK Ltd) for advice and information about nomifensine.

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Pathogenesis of papilloedema and raised intracranial pressure in Guillain-Barré syndrome

Papilloedema and raised intracranial pressure are rare but well-recognised complications of the Guillain-Barré syndrome. The pathogenesis is unknown. If the mechanism were increased accumulation of cerebrospinal fluid large ventricles becoming smaller with clinical improvement would be expected, but if the mechanism were brain swelling the reverse would be true. We have therefore measured ventricular volume from computed tomographic (CT) scans[1 2] of a patient with the Guillain-Barré syndrome (*a*), when headaches and papilloedema were present and (*b*) after recovery.

Case report

A 16-year-old schoolboy was admitted to hospital in April 1980 with a two-week history of weakness in both legs. The weakness then spread to the arms, face, and bulbar and respiratory muscles. He also complained of tingling in his fingers and toes. Examination showed a thin youth with pronounced facial bulbar and proximal limb weakness. The limbs were hypotonic and areflexic with flexor plantar responses. Sensation was not impaired and the fundi were normal.

Nerve conduction studies showed slowing of velocities (common peroneal nerve 30 m/s) consistent with the Guillain-Barré syndrome. Lumbar puncture yielded cerebrospinal fluid at 160 mm H_2O and containing protein 2·2 g/l and no cells. Paul-Bunnell test gave a negative result, serum lead concentration was normal, and no excess of porphyrins was detected in serum, urine, or faeces. Complement fixation tests showed raised titre against measles virus (1024/1024), and complement components C4 and factor B were very low. Over the next few weeks bulbar and respiratory function improved but severe limb girdle weakness persisted.

Ten weeks after presentation the patient developed nausea, vomiting and headache, and bilateral papilloedema. CT scan showed no evidence of any mass lesion, and the ventricular volume was 18·6 ml. Cerebrospinal fluid pressure was 330 mm H_2O with a protein concentration of 3·6 g/l and 2×10^6 white cells/l (2/mm^3). The headaches improved after the lumbar puncture, and a course of six plasma exchanges resulted in a dramatic improvement in strength.

When reviewed in September he was well with no headaches and the papilloedema had resolved. CT scan showed subjectively smaller ventricles with a volume of 5·2 ml.

Comment

Both decreased absorption of cerebrospinal fluid[3] and cerebral oedema[4] have been suggested to explain the raised intracranial pressure that may occur in the Guillain-Barré syndrome. The sometimes inconsistent relationship between raised intracranial pressure and cerebrospinal fluid protein concentration, the inability to produce an animal model by injecting protein into the intrathecal space, and the rarity of raised intracranial pressure as a complication of the syndrome militate against increased cerebrospinal fluid protein as a cause of decreased absorption.[5] Brain swelling appeared to be an attractive hypothesis, especially after Joynt's[4] case report with biopsy findings that he considered to be in keeping with cerebral oedema.

In our patient the reduction of ventricular volume from 18·6 ml to 5·2 ml with resolution of the papilloedema suggests that symptoms had been caused by an accumulation of cerebrospinal fluid. That absorption of cerebrospinal fluid is impaired by excess protein alone is disputed, so an alternative mechanism must be sought. In four other patients with Guillain-Barré syndrome without papilloedema we found no abnormalities in the serum complement. In our patient possibly an immunological disturbance with activation of the classical and alternative complement pathways resulted in impaired cerebrospinal fluid absorption at the arachnoid villi or, alternatively, increased production of cerebrospinal fluid at the choroid plexus. This would suggest that patients with Guillain-Barré syndrome who have a relapsing course and develop papilloedema are immunologically different from patients with conventional symptoms of polyneuropathy alone.

We thank Miss Margaret Matheson, senior physicist, without whose invaluable help the ventricular volumes could not have been measured.

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