A case of herpes zoster associated encephalitis with rapid response to acyclovir

J.S. Cheesbrough¹, R.G. Finch¹ and M.J. Ward²

Departments of ¹Microbial Disease and ²General Medicine, City Hospital, Nottingham, NG5 1PB, UK.

Summary: A case of herpes zoster encephalitis which responded very rapidly to acyclovir is presented. The differential serum: cerebrospinal fluid antibody response was followed and its value in making the diagnosis is discussed. The penetration of acyclovir into the cerebrospinal fluid was measured, and found to be in agreement with predicted values.

Introduction

Herpes zoster is common in the immunosuppressed host and may undergo dissemination. Neurological complications are well recognized but encephalopathy is rare (Jemsek *et al.*, 1983). There have been no controlled studies reporting the response of herpes zoster associated encephalitis (HZAE) to anti-viral agents; the response to vidarabine has been variable (Jemsek *et al.*, 1983). We report a patient who had a rapid response to acyclovir.

Case report

A 30 year old woman was admitted in December 1982 with a 48 h history of chest pain associated with increasing somnolence and confusion. There was no history of headache, vomiting or seizures. In June 1981 she received a renal allograft having been on dialysis for 4 y for chronic glomerulonephritis. Despite oral azathioprine 100 mg/d and once weekly intramuscular methyl prednisolone 100 mg she developed chronic rejection with a mean creatinine of 356 mmol/l for the preceding three months.

On admission she was febrile and had a typical zoster rash in the right T2 dermatome with no cutaneous dissemination. She was barely responsive to commands with a Glasgow coma scale (GCS) score of ten (Teasdale & Jennett, 1974). Four hours later she responded slowly but appropriately to simple questions, yet by twelve hours she was obtunded with dysconjugate gaze, GCS score of four. There was no meningismus or other neurological sign.

Investigations on admission revealed a

haemoglobin of 9.5 g/dl and a white cell count of $9.2 \times 10^9/l$ with a normal differential. The plasma sodium was 139 mmol/l, potassium 4.9 mmol/l, urea 29.1 mmol/l, creatinine 632 $\mu\text{mol/l}$ and bicarbonate 9 mmol/l. Liver function tests were normal except for an elevated glutamic pyruvate transaminase of 41 international units/l. She was acidotic with an arterial pH of 7.04, base excess -22 , $\text{PaO}_2/\text{PaCO}_2$ 14.5 kPa and a PaCO_2 of 4.30 kPa. The chest radiograph was normal and a heat computed tomography (CT) scan showed symmetrical cerebral oedema with no focal abnormalities. A urine drug screen revealed no significant finding. The cerebrospinal fluid (CSF) was examined on three occasions (Table I). Varicella-zoster virus was isolated from the skin vesicles but not the CSF.

Treatment was initiated with intravenous hydrocortisone and bicarbonate. The following day because of deepening coma intravenous acyclovir was commenced with a single loading dose of 10 mg/kg, followed by 5 mg/kg/d for ten days. Improvement by 24 h was dramatic, with a GCS score of 14, and after 48 h she was fully recovered.

Discussion

Encephalitis occurs in up to 5% of patients hospitalized with herpes zoster, usually complicating disseminated disease (Marzur & Dolin, 1978). The clinical picture is variable and non-specific, with mild confusion, hallucinations, and stupor predominating. Progression to coma is unusual, and death rare. Although coma is usually brief (1–4 days) complete mental recovery is often delayed particularly in the immunosuppressed patient in whom the mean duration of neurological symptoms is 22 days. The CSF

J.S. Cheesbrough, M.R.C.P.; R.G. Finch, M.R.C.P., M.R.C.Path.; M.J. Ward, M.R.C.P.
Accepted: 22 December 1983

Table I Results of serial CSF samples including specific antibody index and acyclovir penetration.

Day of illness	2	6	11
pressure/cm of CSF	35	14	16
red blood cells/mm ³	175	105	250
polymorphs/mm ³	1	0	0
lymphocytes/mm ³	3	0	0
CSF/plasma glucose (mmol/l)	4.7/5.9	2.8/3.8	4.4/6.0
total protein (g/l)	0.5	0.4	0.6
CSF/serum albumin (g/l)	0.31/27	0.21/28	0.19/31
¹ CSF/serum V-Z titre	16/4096	32/8192	64/8192
² Antibody index	0.34	0.52	1.27
CSF/plasma acyclovir μ mol/l	not done	0.06/0.14	4.16/19.7
CSF/plasma acyclovir (%)		43	21

¹IgG antibody against V-Z virus was determined by immunofluorescence and is expressed as reciprocal titre. IgM was not detected in the CSF and is excluded from result.

²Antibody index = CSF titre/serum titre $\times$ serum albumin/CSF albumin. V-Z = varicella-zoster.

may be normal but a mild lymphocytic pleocytosis is more common with an elevated protein and a normal glucose. Support for the diagnosis can be sought serologically. The presence of antibody in the CSF detected by indirect immunofluorescence has been strongly associated with encephalitis and is rarely found in patients lacking neurological involvement (Gershon *et al.*, 1980). In an attempt to distinguish local antibody production within the central nervous system (CNS) from that due to diffusion across the blood/CSF barrier an index has been described, (Klapper *et al.*, 1981). In herpes simplex encephalitis a value above 1.9 is diagnostic. The maximum value in our patient was 1.27. This suggests a degree of local antibody production which, although non-diagnostic by herpes simplex encephalitis criteria has yet to be evaluated in herpes zoster infections.

The simultaneous plasma and CSF acyclovir levels show 43% penetration in the second sample taken 22 h after infusion and 21% in the final sample collected 1 h post infusion. The only other published report which

used predicted plasma levels indicated approximately 50% penetration (Blum *et al.*, 1982).

The administration of corticosteroids and the correction of the acidosis may have contributed to her improvement. However the clinical prodrome, abnormal CSF and CT scan with the apparent local production of specific antibody in the CSF all support the diagnosis of HZAE rather than a metabolic encephalopathy. Whether HZAE is due to direct viral invasion of the CNS, or a related immune phenomenon, remains uncertain. The rapid recovery that accompanied acyclovir suggests that direct viral invasion of the CNS was the cause of HZAE in this case.

Acknowledgements

We thank Dr R. Burden for allowing us to report his patient, and Professor M. Longson, Dr D. Craddock-Watson, and Dr S. Pugh for assistance with the viral serology and Dr D. Brigden at Wellcome Research Laboratories for performing the acyclovir assays.

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