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Case report

Cerebral vasculitis associated with shingles

J D M Edgar, J J Crosbie, S A Hawkins

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Shingles is a common manifestation of infection with herpes zoster virus (more correctly varicella-zoster virus) in middle-aged or elderly people. We describe three patients who developed brain stem encephalitis and cerebral vasculitis due to infection with this agent during a 12-month period.

CASE 1

A 77-year-old lady initially presented to her family doctor in January 1987. She complained of a painful left ear with associated hearing loss and dizziness. There were vesicles on the left pinna, and she had a left lower motor neurone facial palsy. She was treated for five days with oral acyclovir and topical idoxuridine, but her symptoms did not resolve. Two weeks after the onset she became ataxic, with double vision and nausea. She was admitted to an ear, nose and throat ward, and a neurological opinion was sought.

She was fully alert and orientated. There were vesicles on the left pinna. She had gaze-evoked nystagmus on horizontal and vertical gaze, maximum on left lateral gaze. There was a complete left lower motor neurone facial palsy. There was a right carotid artery bruit. There were no other cranial nerve lesions. Power and sensation were fully intact, tendon reflexes were symmetrical but the left plantar response was extensor. She had marked truncal ataxia and left-sided incoordination. Computerised tomography scan of the head showed evidence of cerebral atrophy but no focal lesion.

Treatment with heparin and acyclovir was started intravenously. Her ataxia showed a steady improvement but left tarsorrhaphy was required due to the absent corneal reflex. At review five months later she was walking unaided though her balance was poor. The left lower motor neurone lesion persisted.

CASE 2

A 66-year-old man first presented to his family doctor in March 1987 with left-sided ophthalmic herpes zoster. Two days later he developed drowsiness, confusion, slurring of speech, left-sided facial weakness and a tendency to fall to

Department of Medicine, The Queen's University of Belfast, Institute of Clinical Science, Belfast BT12 6BJ.

S A Hawkins, BSc, MB, MRCP (UK), Senior Lecturer in Neurology and Consultant Neurologist.

Royal Victoria Hospital, Belfast BT12 6BA.

J D M Edgar, BSc, MB, MRCP (UK), Senior House Officer in Neurology.

J J Crosbie, MB, BCh, BAO, Senior Registrar in Neuropathology.

Correspondence to Dr Hawkins.

the left side. He was admitted to an ophthalmology ward, where he was found to have iritis in the left eye, left-sided facial weakness and an almost complete restriction of upward gaze. He was treated with oral acyclovir, prednisolone eye drops and mydriatics for five days. After discharge, his unsteadiness and facial weakness gradually improved but he was troubled by post-herpetic neuralgia.

Six weeks after the onset his condition deteriorated, with return of the unsteadiness and facial weakness. He also complained of headache, double vision and speech was again slurred. On admission to the neurology ward he was drowsy and mildly confused with marked dysarthria. His left pupil was dilated therapeutically. Upward and downward gaze was restricted to a flicker, and there was restriction of conjugate gaze to the left with nystagmus. He had a right-sided upper motor neurone facial nerve lesion, right arm weakness and mild heel-shin ataxia. Power in the lower limbs was full. Reflexes were symmetrical and plantar responses flexor. Sensation was fully intact. CT scan showed considerable enlargement of the lateral and third ventricles and of the cerebral sulci consistent with cerebral atrophy, probably long-standing. There was a small focal area of low density in the left basal ganglia bordering on the left internal capsule, consistent with infarction.

He was considered to have brain stem encephalitis secondary to varicella-zoster infection and treatment initiated with intravenous heparin and acyclovir was continued for seven days. He made a gradual improvement and remained an in-patient for four weeks. At discharge his speech was clear, the right-sided weakness was barely detectable, and his range of eye movement had improved. Confusion and drowsiness had disappeared. The post-herpetic neuralgia has remained a persistent problem. At review 16 months after the onset he had regained his previous normal mental state, there was no ataxia, but elevation of both eyes was restricted to 30% of normal.

CASE 3

A 72-year-old lady presented to the neurology department in March 1987. Twelve days previously she had experienced left-sided facial pain, followed by the development of a herpes zoster rash on the ear and loss of sensation on the left side of the face. She became unsteady on her feet and was confined to bed. She was fully alert with slurred speech. There was minimal gaze-evoked nystagmus to the left side and a partial left lower motor neurone facial palsy. She had a vesicular rash on the left side of her face and diminished sensation in the left fifth nerve territory. Examination of the limbs showed cerebellar ataxia, worse on the left side, and bilateral distal weakness. Plantar responses were flexor and sensation was intact. These features were consistent with the Ramsay–Hunt syndrome, with additional brain stem signs. She was treated with intravenous acyclovir 10mg/kg for ten days.

During the first week she began to complain of paraesthesia in the left arm and progressive weakness of the left side. CT scan excluded the possibility of intracerebral haemhorrhage, and it was decided to add intravenous heparin. Her weakness showed a sustained improvement but two weeks later she had an unexpected cardiac arrest and died. (Figs 1, 2).

Autopsy showed severe stenosing atherosclerosis of the left anterior descending coronary artery with recanalised thrombus. In the brain and spinal cord there was generalised meningoencephalitis with lymphocytic infiltration of the leptomeninges and of the walls of small meningeal and cerebral blood vessels. No

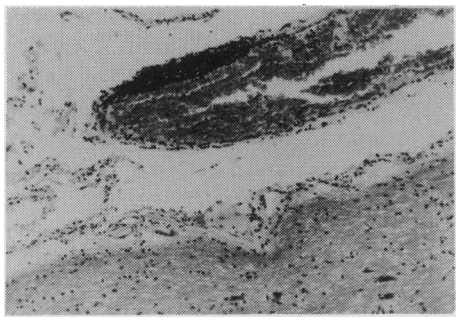

Fig 1. Section of brain stem showing lymphocytic infiltration in the meninges and in the wall of a meningeal blood vessel. Several neurones near the surface of the brain show degenerative changes. HE X100.

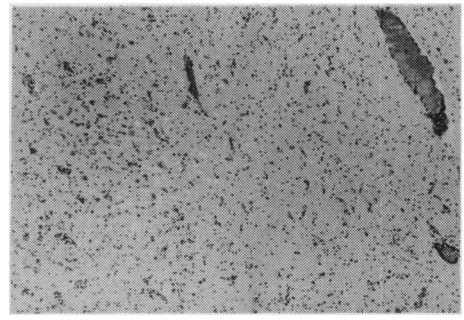

Fig 2. Section of brain stem showing lymphocytic infiltration in the walls of small cerebral blood vessels and capillaries. There are areas of localised oedema and mild glial reaction, and the neurones show focal chromatolysis and neuronophagia. HE X60.

giant cells were present and there was no evidence of a systemic vasculitis. The internal carotid arteries showed no inflammation and there was no generalised thrombosis. The brain stem showed a localised area of oedema, focal chromatolysis and neuronophagia, with lymphocytic cuffing of small blood vessels. The lumbar root showed marked neuronal swelling and there was demyelination of the spinal cord, which could be attributed directly to the virus or could represent neuronal damage due to oligaemic hypoxia secondary to the vasculitis.

DISCUSSION

These patients all demonstrated the development of neurological features after a latent period following varicella-zoster virus infection. The development of brain stem encephalitis is well recognised, but these cases highlight the importance of cerebral vasculitis, which is less often recognised and has important implications for treatment. Each case not only showed the signs of brain stem encephalitis; two developed ipsilateral weakness and in Case 2 a contralateral hemiparesis. There was therefore clinical suspicion of cerebral thrombosis in all, and in Case 3 pathological evidence of vasculitis with selective neuronal necrosis.

In 1982 Doyle et al[1] reported a case of ophthalmic herpes zoster followed by contralateral hemiplegia which at first responded to steroids, but when these were reduced, culminated in massive cerebral infarction and death. At autopsy the left internal carotid artery was thrombosed throughout with extension into the middle and anterior cerebral arteries. They demonstrated an extensive necrotising arteritis of large and small cerebral vessels and were able to demonstrate herpes-like virions in the smooth muscle cells of the middle cerebral artery. Gasperetti and Song[2] reported a 79-year-old woman with right-sided ophthalmic herpes zoster and a left-sided hemiplegia. Autopsy showed lymphocytic infiltration of the meninges, thrombosis of meningeal arteries with arteritis, and lymphocytic infiltration of the semilunar ganglia on the affected side.

Eidelberg et al[3] studied three patients with large vessel cerebral vasculopathy following herpes zoster. At autopsy or brain biopsy all showed large vessel occlusions without notable inflammatory or granulomatous change. Varicella-zoster virus antigens were demonstrated in the media of the affected arteries, but

little or no inflammation was associated with the foci of virus antigens. The distribution of the vascular lesions in the two patients with ophthalmic herpes zoster was consistent with what is known of trigeminovascular connections. Patients with ophthalmic herpes zoster and contralateral hemiparesis have demonstrated a stereotyped pattern of angiographic abnormalities, and they concurred with the anatomical route of infective spread suggested by Gasperetti and Song. Their histopathological findings were consistent with thrombosis *in situ* of large cerebral vessels as opposed to vasculitis, and they concluded that the therapy of choice would be heparin.

Thomas and Howard [4] estimated the incidence of encephalitis to be 0·25% of all cases of herpes zoster infection. The risk increased in immunosuppressed patients with disseminated zoster, elderly patients, and for zoster affecting the cranial nerves and cervical and upper thoracic cord segments. The clinical manifestations of encephalitis usually develop about nine days after the rash,[5] but may precede the rash by as much as 30 days, begin simultaneously or occur as long as six weeks later. Herpes zoster-associated encephalitis is suggested by the presence of the characteristic rash, or by a recent history of zoster. Lumbar puncture frequently shows lymphocytic pleocytosis with elevated protein and normal glucose. The clinical picture is variable, onset is usually acute but may be gradual. Headache is frequent with neck rigidity and fever, impairment of consciousness with hallucination, confusion or delirium. In contrast to encephalitis following varicella infection, convulsion, coma and ataxia are said to be uncommon. Cranial nerve paralysis may develop during the encephalitis illness, as may features of myelitis, hemiparesis and choreoathetoid movements. Forty per cent of uncomplicated varicella-zoster virus infection will show cerebrospinal pleocytosis possibly reflecting ganglionitis of the involved nerve root.[6] It is interesting to speculate why such patients do not show signs of meningism.

The pathogenesis of the encephalomyelitis is not fully understood, but there are two main theories — direct viral invasion from the infected sensory ganglia, and an immunologically mediated post-infectious mechanism. The evidence for direct viral invasion is in two cases where inclusion bodies and varicella-zoster virus particles have been demonstrated in glial cells. The frequently observed delay between rash and symptoms may be evidence of an autoimmune post-infectious aetiology. The evidence is not conclusive for either mechanism and the two mechanisms are not mutually exclusive.

Our three cases all presented with symptoms which supported a diagnosis not only of brain stem encephalitis but also suggested vasculitis, and in the one case examined at autopsy, cerebral vasculitis was demonstrated histologically. Of more practical importance, we demonstrated definite clinical improvement in all three cases with intravenous heparin as well as acyclovir. The third patient died of an unrelated myocardial infarction, but the other two have shown continued improvement. We suggest that in those patients where intravascular thrombosis consequent on varicella-zoster virus infection is likely, this regimen should be the treatment of choice.

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