Herpes encephalitis and herpetic corneal disease

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Summary
A case of herpes encephalitis is reported in a patient who had cranial irradiation and high dose steroids for a cerebral neoplasm. Before radiotherapy the patient had had herpetic infections of the skin and eye.

Introduction
Little is known about the relationship between herpes encephalitis and recurrent herpetic infections of the eye and skin. A patient is presented who, following a recurrence of herpetic stromal keratitis of the cornea, developed herpes encephalitis. It is suggested that special factors in this case explain the sequence of events, and their therapeutic implications are discussed.

Case report
The patient, a 61-year-old wholesale furrier, presented with a 3-week history of short-term memory loss, inability to concentrate at work and mild occipito-frontal headaches. For many years he had had recurrent herpes labialis. In 1975 he was seen at Moorfields Eye Hospital with a red, painful right eye and a diagnosis of herpetic stromal keratitis with uveitis was made. He was treated with idoxuridine ointment and atropine and steroid eye drops. His keratitis and uveitis resolved, leaving only faint stromal scarring but extensive atrophy of the iris. There was no further recurrence until the present episode.

On presentation at The London Hospital he was alert but disorientated in time and on formal testing his intellectual ability was depressed. Apart from an enlarged unreacting right pupil, which was attributed to his post-uveitic iris atrophy, there were no other abnormal neurological signs. His blood count, skull and chest X-rays were normal. EEG and technetium brain scan suggested a left cerebral hemisphere lesion involving midline structures. Computerized axial tomography showed displacement of the posterior portion of the III ventricle to the right. Deep in the left temporal lobe there was an area of heterogeneous attenuation. After contrast, this area showed homogeneous enhancement in some areas and ring enhancement in others.

On the basis of this report, a diagnosis of a glioma situated deep in the left temporal lobe was made; because of its position, he was treated with dexamethasone and radiotherapy without a biopsy. He initially had an excellent response and he was discharged from the hospital on a reducing dose of dexamethasone, having initially received 3 mg/day. He continued his radiotherapy as an out-patient and received a total dose of 5400 rad (radiotherapy was given in 25 fractions spread over 5 weeks, each fraction was 220 rad). Two weeks after discharge he was readmitted, having collapsed in the radiotherapy department; apart from mild confusion, there were no new neurological signs. His dexamethasone was increased to its original dose of 3 mg/day. The next day he complained that the vision of his right eye was blurred; ophthalmological examination revealed circum-corneal infection and a large active herpetic corneal ulcer. He was treated with atropine drops and idoxuridine ointment; 3 days later his corneal ulcer was much improved. However, his general neurological state continued to deteriorate and he lapsed into coma; severe herpes labialis was now observed surrounding his whole mouth. An EEG showed a severe disturbance of both temporal lobes, more marked on the right side with a mixture of delta and theta elements consistent with a diagnosis of herpes simplex encephalitis. He died 2 days later.

At post-mortem, a neoplasm of the left caudate nucleus was found. Histologically this was a glioblastoma multiforme, and electron microscopy demonstrated herpes virus particles in the right temporal lobe.

Discussion
Whether herpes encephalitis is a primary or secondary infection remains uncertain; few patients are investigated early enough to obtain a baseline antibody level followed by a rising titre as the infection progresses. Serological diagnosis of herpes encephalitis is complicated further if there have been primary infections elsewhere, such as the eye, mouth or skin. Recurrent herpes simplex attacks usually
The route by which the virus reaches the central nervous system (CNS) is unresolved. Animal studies (Johnson, 1964; Wildy, 1967) have shown that the virus can reach the CNS by way of peripheral nerves moving in a centrifetal fashion from one endoneural cell to the next via the cell interspaces; an alternative intra-axonal route has also been proposed (Kristensson, Lycke, Strostrand, 1971). In human encephalitis, it is thought that the common mode of infection is from the nasal mucosa to the olfactory bulb and then to the temporal lobe (Flewell, 1973). This suggestion has been supported by experimental animal studies (Johnson, 1964). The present authors propose that an alternative route may be by direct spread from the trigeminal ganglion. The virus has been isolated from the trigeminal ganglion of cadavers (Baringer and Swoveland, 1973) and from animals with acute (Baringer and Griffith, 1970) and chronic (Stevens, Nesburn and Cook, 1972) corneal infections. Following recovery the virus has been shown to persist in the trigeminal ganglion (Stevens et al., 1972). The trigeminal ganglion lies in close vicinity to the uncus of the temporal lobe, but whether this is the latent reservoir from which patients with herpes encephalitis become infected is uncertain; special factors in the present patient may make this a tenable hypothesis.

It has been suggested that patients with recurrent herpes labialis may have a specific impairment of macrophage migration inhibition and reduced lymphocyte toxicity (Wilton, Ivanyi and Lehnar, 1972). Cell-mediated immunity is further impaired in patients receiving steroids and immunosuppressives and a recurrence of severe herpetic infections has occurred in patients when placed on these drugs (Montgomery et al., 1969).

This patient, on a high dose of steroids with active herpetic disease of his cornea and mouth, was thus at risk from systemic spread.

Radiotherapy had been shown to disturb the blood pain barrier in direct proportion to the dosage received (Clemente and Holst, 1954). Before the onset of encephalitis, the patient had received a dose of 5400 rad. Although the association of herpes encephalitis with a dendritic ulcer and herpes labialis may have been fortuitous, it is suggested that a combination of radiotherapy and steroids facilitated spread of the virus from the trigeminal ganglion to the temporal lobe. Perhaps such a mode of spread may be more common than is generally recognized. Patients with recurrent herpetic infections who are receiving corticosteroids and immunosuppressive drugs and radiotherapy should perhaps be covered with appropriate antiviral drugs.

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References