Progressive multifocal leucoencephalopathy: remission with cytarabine

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SYNOPSIS A patient with a 14 year history of sarcoidosis developed a progressive left cerebral hemisphere lesion. The clinical diagnosis of progressive multifocal leucoencephalopathy was confirmed by brain biopsy and remission occurred after treatment with cytosine arabinoside.

Progressive multifocal leucoencephalopathy (PML) is a rare demyelinating disease which was first described by Åström *et al.* (1958) and viruses have since been found in the cerebral lesions (Zu Rhein, 1969). Two virus types have been identified, Polyoma JC (Weiner *et al.*, 1973) and SV 40 (Padgett *et al.*, 1971; Weiner *et al.*, 1972). The disease usually occurs in patients already suffering from a condition in which the immunological system is in some way compromised. Richardson's review (1970) of 85 cases included 45 with lymphoproliferative disorders, 10 with myeloproliferative disorders, and 14 with granulomatous disorders. The prognosis is poor with a progressive deterioration over less than six months and spontaneous remissions are rare (Åström *et al.*, 1958; Hedley-Whyte *et al.*, 1966). Recently, the nucleic acid base analogues idoxuridine and cytarabine have been used in the treatment of some virus diseases, but remission has been reported in only one treated case of PML (Bauer *et al.*, 1973).

CASE REPORT

This 52 year old nursing tutor was known to have had pulmonary sarcoidosis for 14 years which had been treated with a constant dose of prednisolone 7.5 mg daily for the last seven years. She first noticed weakness of the movements of the right thumb in October 1972 and this was associated with some clumsiness in writing. She was first admitted to

hospital in March 1973 with increasing difficulty in the use of her right hand. There was minimal spasticity at the right wrist and elbow and there was slight wasting and moderately severe weakness of the small muscles of the hand associated with considerable difficulty in fine manipulation. There was minimal weakness of elbow extension and shoulder abduction; the supinator and finger reflexes on the right were pathologically brisk. The neurological examination was otherwise normal.

Radiographs of the skull and cervical spine were normal. Electroencephalography (EEG) showed brief bursts of irregular 2-4 Hz activity with more continuous underlying theta activity in the left frontotemporal region (Fig. 1a). A technetium-99m brain scan and a left carotid angiogram were normal.

After a few weeks back at work she noticed drooping of the right side of the mouth and slight difficulty with speech. She found increasing difficulty in doing the *Daily Telegraph* crossword, her right arm became progressively weaker, and she noticed some tendency to drag the right leg. She was therefore readmitted in July 1973 and was then found to have marked dysphasia with perseveration. Her concentration was impaired and even the most simple conversation was limited to no more than three or four words at a time. Visual fields were full. She had an upper motor neurone type right facial weakness and severe cortical weakness of the right hand and forearm associated with wasting of these muscles. There was moderately severe weakness of elbow extension and shoulder abduction on the right. There was some weakness of the right leg of pyramidal distribution, the right arm and leg were spastic with pathologically brisk reflexes, clonus at the wrist and ankle, and the right plantar response was extensor.

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(Accepted 19 August 1974.)

FIG. 1 (a, top left) *EEG during first admission (2 April 1973)*. (b, top right) *EEG before treatment (27 June 1973)*. (c, left) *EEG after treatment for nine months (31 May 1974)*. See text for description.

Investigations showed a blood haemoglobin level of 12 g/dl and a white cell count of 4 700/mm³, neutrophils 85%; lymphocytes 7%; monocytes 4%; eosinophils 3%; ESR was 10 mm in the first hour. Serum protein level was 59 g/l; albumin 40 g; globulin 19 g/l with normal electrophoretic pattern; immunoelectrophoresis showed IgG 750 mg/dl, IgA 160 mg and IgM 36 mg/dl (all slightly reduced). Lymphocyte transformation to phytohaemagglutinin showed marked depression. Serum antibody titres to mumps S and V were both less than 1/8; Herpes 1/16; Mantoux test was negative at 1/100; serological tests for syphilis were negative. Cerebrospinal fluid was at normal pressure and contained 0.3 g/l protein with no excess of globulin and no cells. Radiographs of the chest showed changes consistent with sarcoidosis and apical tomography confirmed bilateral upper zone fibrosis without cavitation.

FIG. 2 *Pale focal and confluent demyelinating lesions in the cerebral white matter and deep cortex. Luxol fast blue/Nissl, $\times 15$.*

FIG. 3 *Virions and viral filaments in a nucleus (bottom); the virions extend into a membrane bound cytoplasmic network (top). Epon, uranyl acetate/lead citrate, $\times 75\ 000$.*

The EEG showed a marked deterioration and was now grossly asymmetrical with almost continuous 4 Hz activity anteriorly in the left hemisphere with intermittent bursts of 1–2 Hz delta activity in this region (Fig. 1b). The brain scan was again normal. A repeat left carotid angiogram was normal apart from slight displacement of the deep veins indicating minimal dilatation of the left lateral ventricle. Pneumoencephalography showed slight dilatation of the third ventricle (width 1 cm) and slight dilatation

of both lateral ventricles, more evident on the left; the cerebral sulci appeared normal.

A clinical diagnosis of PML was made and a brain biopsy was therefore carried out from the left motor cortex to confirm the diagnosis and for identification of the virus. The brain was obviously atrophied. Approximately 1 cm cube of cortex and subcortical white matter was removed. The white matter was soft and tended to fragment. The material was fixed for histology, electron microscopy, and preserved for virological studies in liquid nitrogen.

There were focal and confluent demyelinated lesions in the white matter and deep cortex (Fig. 2). The lesions showed all the characteristic features of PML as described by Richardson (1970). Their centre lacked myelin and oligodendrocytes, while axons and nerve cells were relatively preserved. The oligodendrocytes in the border of the lesions were abnormal with rounded nuclei enlarged up to 15 μm containing acidophilic inclusions. In the centre of the lesions there were large astrocytes with multiple nuclei and ample cytoplasm with foamy macrophages containing neutral lipid. The white matter and the cerebral cortex away from the lesions were normal apart from some perivascular cuffs of lymphocytes and macrophages. Brain smears, which were available within 10 minutes of the biopsy, showed the same cytological features as the sections. Electron microscopy showed masses of rounded virus particles about 40 nm in diameter and viral filaments about 28 nm in diameter in many of the abnormal oligodendrocyte nuclei. In a few cells the rounded virus particles were found to extend from under the outer nuclear membrane into a membrane lined cytoplasmic network (Fig. 3) and some were seen in the extracellular space.

Biopsy material in liquid nitrogen was sent to the Virus Reference Laboratory, Colindale, for identification of the virus. A 10% suspension of the brain tissue was prepared and inoculated into human fetal brain cells. After an incubation period of seven weeks a virus belonging to the Polyomavirus genus was isolated. This strain was designated COL 2.

A portion of the 10% brain suspension was diluted in tissue culture medium and centrifuged at 18 000 rpm/h and examined by electron microscopy for negatively stained virus particles. Spherical particles with typical polyomavirus morphology were observed. Using the technique of immune electron microscopy (Field *et al.*, 1974) the virus was identified as being antigenetically similar to Polyomavirus JC. It was not related to Polyomavirus BK or simian 40, two other viruses belonging to this genus which have been recently isolated from man.

She has been treated with intermittent five day courses of cytarabine in a daily dosage of 2 mg per kilogram body weight. The treatment was started in

the middle of August 1973 and she has now had 13 courses separated by successive intervals of seven, seven, 14, 21, 28, 35, 35, and 14 days; the last four courses have been at intervals of three weeks. The only side-effect has been slight nausea during the days of administration which has been controlled with prochlorperazine. Throughout this time her haemoglobin, white cell count, and platelet count have been measured repeatedly and have remained within the normal range.

A slight but definite improvement was first noticed soon after finishing the first course of treatment. She was discharged from hospital at the end of the second course and at that time her dysphasia had improved considerably allowing conversation at a 10 to 12 word level. Some power had returned to her right shoulder and right hip flexion was stronger. Six weeks after starting treatment she was able to finish about half the *Daily Telegraph* crossword. In conversation there was occasional perseveration and she would correct herself by association. The facial weakness had improved and she no longer dribbled. After three months she had taught herself to write left-handed, she was reading two novels a week and usually finishing the *Daily Telegraph* crossword. Movements of the right hand remained severely impaired and the arm moderately spastic. There was only minimal weakness of right hip flexion and her gait was normal.

Since returning to work at the beginning of November 1973, just over a year after the onset of her symptoms and about three months after the start of treatment, she has managed her job as a nursing tutor satisfactorily. She has found her recent memory slightly impaired but has been able to give her lectures. The EEG has been recorded at the onset of each course of treatment and first showed a definite improvement about a month after the start of treatment, since when it has shown further improvement (Fig. 1c). The interval between treatments has now been fixed at three weeks because she found that she did not feel very well with longer intervals, although this was not accompanied by any change in her physical signs.

DISCUSSION

This patient has been shown by brain biopsy to fulfil the criteria of PML associated with Polyomavirus JC. The association of a progressive focal neurological disease with localized EEG changes and only minimal evidence of cerebral atrophy in a patient with sarcoidosis and depressed cellular and humoral immunity led to

the diagnosis. The history of mumps in the autumn of 1972 may be relevant. Live mumps vaccine may temporarily depress tuberculin sensitivity (Kupers *et al.*, 1970) and this attack may have compromised her immune state to the extent that PML could develop.

More than 100 cases of PML have been reported. These include only four or five cases with spontaneous remission (Hedley-Whyte *et al.*, 1966; Richardson, 1970). Narayan *et al.*, (1973) have correlated the type of virus with the progress of the disease in 13 cases of PML. The prognosis of those patients with the JC virus was worse (mean survival less than six months) than those with SV 40 (mean survival 20 months).

This patient's improvement began within 10 to 14 days of starting treatment and within three months she was well enough to return to work. In the only other case of PML treated with cytarabine, improvement also occurred shortly after treatment was started. This patient also had sarcoidosis (Bauer *et al.*, 1973). It will be necessary to treat many more patients before improvement can be ascribed to the treatment with any degree of certainty. Brain biopsy is necessary to confirm the diagnosis and identify the virus. In view of the continued underlying immune depression and the doubtful ability of the treatment to eliminate the virus from the brain completely, it may be necessary to continue intermittent chemotherapy indefinitely.

ADDENDUM (February 1975)

Treatment has continued with five day courses of cytarabine (2 mg/kg) separated by intervals of three weeks. No complications from this treatment have arisen. She has continued to improve throughout this time and there is now no evidence of aphasia, minimal facial weakness, moderate spastic weakness of the right arm, function of her hand remains severely impaired, there is no weakness in the right leg. As the spastic weakness improved, so an obvious cerebellar ataxia became apparent in the right arm, presumably due to involvement of crossed rubro-thalamocortical cerebellar pathways.

We are grateful to Mr J. J. Maccabe who carried out the brain biopsy and to Dr Sheila Gardener for isolation and identification of the virus.

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