troencephalogram (EEG) showed a diffuse monorhythmic 9–12 Hz activity of 50 μV amplitude, with no reactivity to painful stimulation. Multi-drug screening tests established intoxication with a benzodiazepine later identified as flunitrazepam.

On the second day the patient gradually regained consciousness. A repeat EEG at that time was normal. After recovery he admitted an attempt at suicide taking 25 tablets each of 2 mg of flunitrazepam.

This case presented two features which have not previously been reported in benzodiazepine-intoxication. Firstly, the asymmetrical neurological signs suggested this patient had a structural brainstem lesion which can not always reliably be excluded by CT scan. This emphasises the necessity of multi-drug screening tests in every patient with “coma of unknown origin” even in the presence of lateralizing signs. Secondly, an alpha coma is relatively rare and has been associated with hypoxic encephalopathy of primary brainstem lesions. Occasionally however this type of EEG pattern results from an overdose of drugs such as glutethimide, barbiturates and amytirpiline.

Unlike the patients with hypoxic encephalopathy, a drug-induced alpha pattern coma has a good prognosis. This case demonstrates that flunitrazepam also should be included in the list of drugs that can cause alpha pattern coma.

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References

Distant metastases from a malignant glioma: unusual complications associated with treatment of a glioblastoma: distant metastases and focal white matter degeneration

Sir: Gliomatous metastases have been found in the liver, bone, lung, pleural cavity, pericardium and lymph nodes. Only rarely do patients develop bone marrow invasion with myelofibrosis and symptomatic anaemia. We report the second such case in which pancytopenia resulting from marrow invasion was the primary clinical presentation. In addition, white matter degeneration due to the effects of radiotherapy and possible chemotherapy caused a major diagnostic dilemma. The importance of glial fibrillary acid protein staining to confirm the diagnosis of metastatic glioma while the patient is alive is demonstrated.

A 52 year old business executive was well until 1972 when he suffered a generalised seizure. A complete evaluation was negative aside from an EEG which revealed left frontal slowing. He remained neurologically intact aside from occasional right focal motor seizures until 1980 when he developed mild aphasia. A CT scan revealed a contrast enhancing lesion in the left parietal region. Tumour removed by subtotal resection in April 1980 was considered to be a Grade III astrocytoma. The patient continued to worsen and in June 1980, an extensive resection was performed. Between July 18, 1980 and August 21, 1980 he received 5000 rads whole brain radiotherapy in 25 fractions. A boost of 1000 rads was delivered in five fractions to the left frontal region. Following this the patient received six three day courses of intravenous BCNU given 6 weeks apart from October 1980 to June 1981 totalling 1600 mg/m². Procarbazine was given daily from July 1981 to November 1981 and again from January 1982 to February 1982. He was admitted to the Roger Williams General Hospital on July 2, 1982 because of increasing rightsided weakness and lethargy. Physical examination was remarkable only for a moderate aphasia and a mild right hemiparesis. Laboratory values included: WBC, Hgb 11.8% mg HCT 32.9%, MCV 96, Platelets 197,000. The blood smear appeared normal. Fe/TIBC = 44/165. SMA6, VDRL, PT, APTT and SMA12 were normal aside from: lactate dehydrogenase 418 U/l (normal 80–210), alkaline phosphatase 438 U/l (50–260), serum glutamic-oxaloacetic transaminase 31 U/l (5–30), cholesterol 385 mg% (160–300). Stool was negative for occult blood. Chest radiographs revealed an abnormal linear density in the right lung base thought to be either scarring or a subsegmental area of atelectasis. The right sixth rib demonstrated a posterolateral fracture and the bones were osteopenic. Contrast enhanced cerebral CT scan revealed bilateral ventricular enlargement, left greater than right, with a semicircular ring enhancing lesion adjacent to the skull in the left superior anterior region and a small left frontal enhancing nodule abutting the ring. He was started on dexamethasone with significant improvement of his intellectual function and to a lesser degree his right sided weakness. Over the next 2 months, the patient’s haematological function worsened, with slowly declining platelets and haemoglobin levels. Intermittent transfusions were required to maintain a haematoctrit above 20. Alkaline phosphatase continued to be elevated. Chest radiograph was interpreted as showing diffuse bony metastases. Seizure activity became more difficult to control so that carbamazepine was substituted for primidone. Dexamethasone was increased to 6 mg qid because the aphasia and right sided weakness became worse. A repeat CT scan in October 1982 revealed no significant interval change however.

Several attempted bone marrow aspirates and biopsies failed to produce adequate specimens for diagnosis. A biopsy specimen in November 1982 showed a monomorphic proliferation of a malignant cell line of undetermined type. He continued to require transfusion of both blood and platelets. His neurological status continued to deteriorate, although repeat CT scan again did not reveal any significant change. The patient died in December 1982 from complications of pancytopenia and adult respiratory distress syndrome.

The general necropsy revealed a nonmalignant pleural effusion, early pneumonia, and an old myocardial infarction. The spleen revealed small areas of extra-medullary haematopoiesis. The vertebral bones were infiltrated by a white tissue which on microscopic examination was found to be composed of small undifferentiated tumour cells identical to those noted in the surgical brain specimen of 4/22/80. These cells were positively stained with immunoperoxidase for glial fibrillary acid protein. In the brain, a cavitative necrotic lesion of about 4 cm surrounded by a brownish gliotic zone was found in the left fronto-parietal region. There was a mild yellowish discoloration of the adjacent white matter of the centrum semiovale. The left lateral ventricle was slightly dilated at the frontal end due to gliosis of the adjacent white matter. The cerebellum, pons and medulla showed no significant change. External to the necrotic area was a zone of intense gliosis in which thick-walled blood vessels were seen. Spreading from the edge of the cavity was an area of graded loss of myelinated nerve fibres, ranging from total destruction to a subtle spongiosis of the white matter. There was, however, widespread blood vessel thickening even in areas where there was...
only a mild degree of nerve fibre loss. The corpus callosum showed severe loss of nerve fibres, increased numbers of glial cells, reactive astrocytes and focal necrosis. The caudate nucleus and internal capsule on the left side were normal. Only mild neuronal loss was seen in the left globus pallidus. The cerebellum and the whole right hemisphere were normal. Scattered giant axonal spheroids were present in the posterior portion of the rostral medulla. No evidence of glioma was found. The abnormalities described were diagnostic of a widespread leukoencephalopathy due to radiation and/or chemotherapy.

Most extraneural metastases from gliomas occur after craniotomy although at least eight cases had been reported, in the absence of surgery. The diagnosis of systemically metastatic central nervous system tumours is not easy to make and is probably not often considered. Weiss established four criteria: first, the presence of a single tumour which is histologically characteristic of a primary glioma; second, a clinical history indicating that initial symptoms were due to this tumour; third, a complete necropsy excluding the possibility of any other primary site; and fourth the identical morphology of the CNS tumour and the distant metastases with due allowance for differences in degree of anaplasia. The use of glial fibrillary acidic protein, a cytoplasmic marker for identifying glial cells, provides a more definitive histological characterisation of tumours of neural origin and allows for the diagnosis of metastatic glioma in the absence of the classical criteria.

The present case is unique in that three rare events in the treatment of a glioblastoma occurred in concert, namely systemic metastasis, cure of the glioma at the primary site and treatment induced leukoencephalopathy. Death was from complications secondary to bone marrow infiltration by glioma cells. The patient developed progressive neurological dysfunction from white matter degeneration following radiation and chemotherapy while the primary tumour appeared to have been eradicated. The major problem during the patient’s last several months related to his pancytopenia. The diagnosis of metastatic glioma was not considered until necropsy. Marrow suppression was initially thought due to chemotherapy. Terminally, when a bone marrow biopsy produced malignant cells, a second malignancy was thought to have developed. This case suggests that combined radiation and chemotherapy were effective in treating the glioma but were the cause of white matter degeneration. As prolonged survival becomes more common with this tumour, clinicians may see an increasing number of similar complications. Staining for glial fibrillary acidic protein may preclude a lengthy and costly search for a second primary malignancy.

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Optico-acoustic atrophy in distal spinal muscular atrophy

Sir: The triad of hereditary motor and sensory neuropathy, optic atrophy and deafness was first reported in a kindred of two brothers and their nephew by Rosenburg and Chutorian in 1967.1 A similar clinical syndrome in a brother and sister was described in 1970.2 But for the sensory manifestations, the clinical features of hereditary motor and sensory neuropathy might be confused with the distal form of spinal muscular atrophy. We report a case of distal spinal muscular atrophy associated with optico-acoustic atrophy and believe that this association has not been previously described.

The patient presented at the age of 10 years with visual impairment. Three years later she became deaf and was shown to have severe bilateral sensori-neural deafness 12 years later. At this time she also complained of clumsiness of her hands and was found to have distal muscle wasting and weakness in both upper limbs. There were no sensory signs and the deep tendon reflexes were retained.

Fifty-one years after initial presentation, she was unable to hear and understand speech. Visual acuity (aided) was 6/60, N10, bilaterally. The symptoms and signs in the upper limbs remained unchanged. There was no family history of neuro-muscular disease, blindness or deafness and she had had no children.

Examination revealed bilateral optic atrophy with no pigmentary retinopathy. There was marked wasting and weakness of the small muscles of the hands and forearms with preserved reflexes. There were no sensory signs and no thickened peripheral nerves.

Glucose tolerance test, serum thyroxine and creatine kinase were normal. No ana(thocytes were seen in the peripheral blood. Cervical spine radiographs showed mild cervical spondylosis. CSF protein and gamma globulin levels were normal. Nerve conduction studies showed normal motor and sensory conduction velocities in upper and lower limbs. Sensory action potentials were of normal amplitude (right ulnar 10 µV, right sural 12 µV). Electromyography showed evidence of chronic partial denervation with polyphasic potentials and giant units to 12 mV in proximal and distal muscles in upper and lower limbs. Spontaneous activity was sparse. Muscle biopsy (left deltoid) showed fibre-type grouping compatible with the electromyographic findings. Visual evoked potentials (checkerboard pattern reversal) were delayed bilaterally. The

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