

Short report

Hypercalcaemia associated with cerebral vasospasm causing infarction

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SUMMARY Central nervous system disorders are not uncommon in patients with hyperparathyroidism and hypercalcaemia. Usually these consist of neuropsychiatric disturbances but acute encephalopathies and seizures may occur. A rare manifestation is cerebral infarction. A patient is presented with neuroradiological evidence of infarction caused by cerebral arterial spasm which appears related to hypercalcaemia due to hypervitaminosis D. Arterial spasm is suggested as a possible aetiological factor in focal neurological lesions associated with hypercalcaemia.

The psychiatric manifestations of hypercalcaemia have been discussed by several authors.¹⁻⁷ Included are bizarre confusional states with delirium and hallucinations, lethargy, drowsiness, impairment of intellectual functions, headache and systemic symptoms such as nausea and vomiting. Coma occasionally supervenes. Apart from mental dysfunction, generalised hyperreflexia is usually the only other neurological sign. The EEG usually reveals non-specific slow wave activity⁸ and the CSF may show an elevated protein.⁹

Seizures, both generalised¹⁰ and focal¹¹ and acute encephalopathy with permanent neurological deficit¹² have been described in association with hypercalcaemia.

One of the less common neurological features associated with hypercalcaemia is cerebral infarction. In 1962, Fentz¹³ reported a 12 year old boy who presented with hypercalcaemia and mild systemic symptoms followed by acute coma, hypertension and left hemiparesis. Recovery occurred within a day but was followed by a similar episode with right hemiparesis from which the patient also recovered. Andersson and Lindholm¹⁴ reported a 67 year old male who developed left hemiparesis which resolved over a week. Bostrom and Alverdy¹⁵ reported 12 patients with evidence of major stroke and five

with minor stroke who were found to have hypercalcaemia due to parathyroid adenomas, parathyroid hyperplasia or parathyroid carcinoma.

As yet apparently no mechanism has been advanced to explain either the neuropsychiatric features or the episodes of focal neurological disturbance seen during hypercalcaemia. The following case is presented since it reveals the mechanism of how this hypercalcaemic patient developed cerebral infarction.

Case history

DT, a 52 year old left handed Australian female, had been well until becoming thyrotoxic in August, 1977. Thyroidectomy in December, 1977 resulted in hypocalcaemia after operation, for which she was commenced on replacement therapy consisting of Calcium 1 tablet (400 mg as a mixed salt) three times daily and calciferol 1.25 mg (50 000 units) three times daily.

Following surgery she remained euthyroid and clinically well until three weeks prior to admission in July 1978 when she began experiencing severe headaches with vomiting and polyuria.

Examination on admission revealed mild dehydration, blood pressure 150/100 mm Hg and pulse 64 per minute, drowsiness, and moderate generalised hyperreflexia.

Serum calcium was 4.3 mmol/l (normal range 2.05–2.55). Serum sodium was 143 mmol/l, potassium 2.7 mmol/l, chloride 87 mmol/l and

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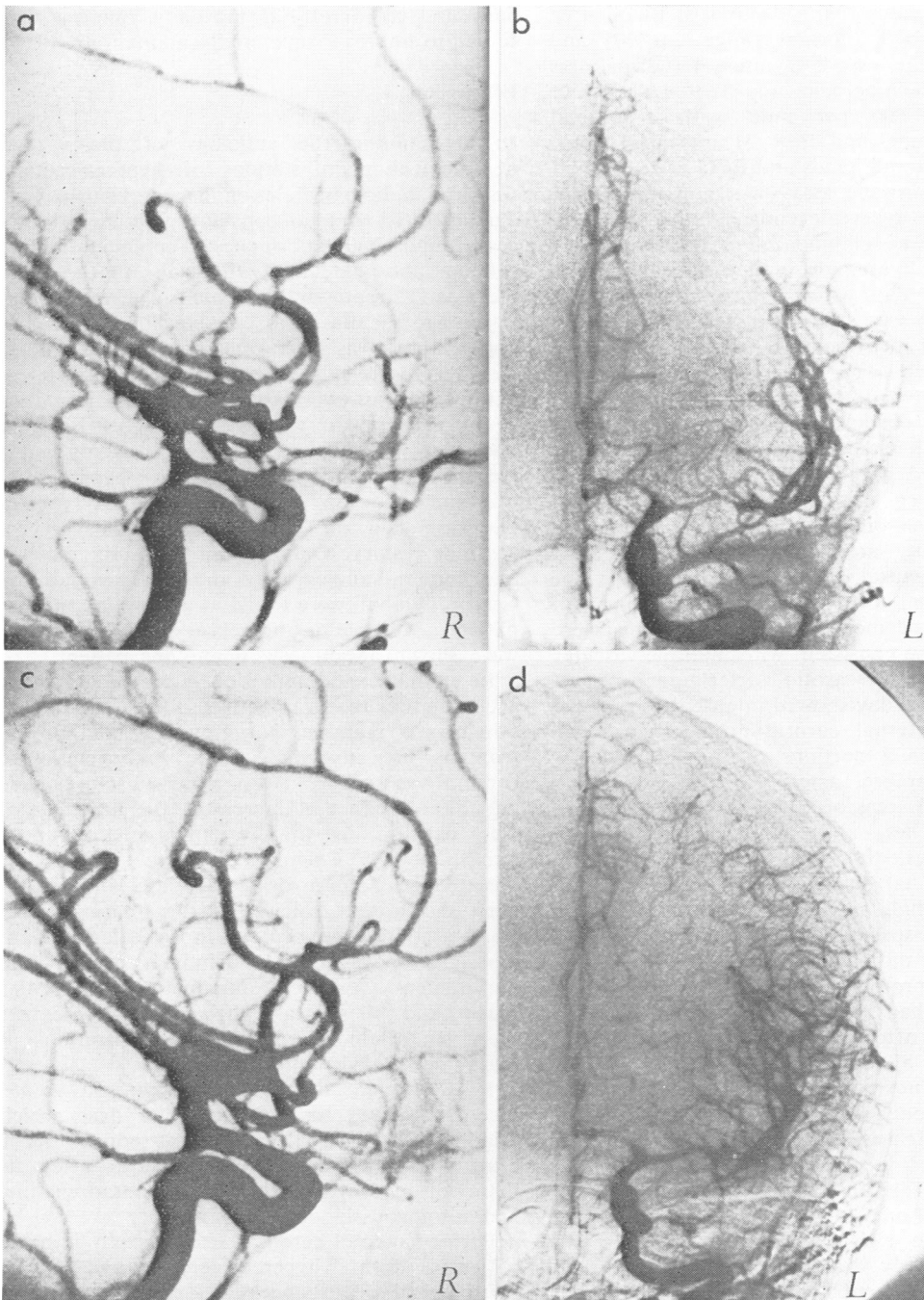


Figure (a) Initial right common carotid angiogram (CCA) showing spasm of the internal carotid artery (ICA) before and after origin of the posterior communicating artery. (b) Initial left CCA showing spasm of the middle cerebral artery (MCA), proximal to the trifurcation, and of the anterior cerebral artery. (c) Repeat right CCA with minimal spasm of the distal ICA. (d) Repeat left CCA now within normal limits.

bicarbonate greater than 50 mmol/l. Blood urea was 15.6 mmol/l (normal range 2.0–7.0) and serum creatinine was 0.37 mmol/l (normal less than 0.11). Haemoglobin was 12.9 g/dl, white cell count 11 600 per mm³ with a normal differential count, and ESR 31 mm in 1 hour. X-rays of chest and hands and ECG were normal. Parathyroid hormone assay was not elevated in relation to the hypercalcaemia.

Treatment was commenced with intravenous normal saline, frusemide, and prednisone. However, on the day after admission (when the serum calcium was still 3.6 mmol/l) the patient complained of heaviness in her left leg. Over the next seven days this progressed to left hemiparesis involving face, arm and leg, associated with cortical sensory loss and fluent dysphasia. Both plantar responses were extensor.

Computerised tomographic (CT) brain scan performed seven days after admission showed cerebral oedema on the right side with at least two low density areas, one high in the right parietal parasagittal cortex and another in the occipital region. There was no alteration with contrast enhancement and the changes were considered to be consistent with multiple vascular defects. Bilateral carotid arteriography performed the same day showed intense spasm of the distal right internal carotid artery (figure (a)) and the proximal portions of the left anterior and middle cerebral arteries (figure (b)). Additional localised areas of spasm were seen in distal cortical branches, and significant slowing of blood flow transit time through both hemispheres was present. That day lumbar puncture was performed to exclude subarachnoid haemorrhage as a cause of vasospasm. This revealed normal pressure, no abnormal cells or xanthochromia and a normal CSF protein of 0.45 gm/l. The serum calcium level had remained abnormally elevated for four days after admission but then became normal as did all other electrolytes.

Over the next three weeks improvement occurred and only mild pyramidal and dominant parietal lobe features remained at the time of discharge.

A second CT brain scan performed two weeks after the initial one showed mild residual cerebral oedema in the right hemisphere and the two regions previously described now showed some contrast enhancement consistent with infarction. Repeat carotid arteriography performed at the same time (figure (c, d)) showed a marked decrease in the degree of arterial spasm present. At that stage serum calcium was 2.3 mmol/l and supplementation consisted of calcium 1 gm twice

daily and calciferol 1.25 mg daily. She has continued to improve since, and remains well.

Discussion

In determining the aetiology of the various neurological manifestations of hypercalcaemia, no clear radiological lesion has previously been demonstrated and no constant pathological process found. Bartter³ suggested precipitation of calcium phosphate and other salts in the brain whereas Karpatis and Frame¹⁶ suggested that hypomagnesaemia was responsible. Cerebral angiography was performed two hours and a week respectively after the development of hemiparesis in two patients and was found to be normal.^{13, 14} In the large series of Bostrom and Alveryd¹⁵ only six of the 17 patients had a reasonable time relationship between hypercalcaemia and the onset of the neurological features and also had no serious pre-morbid cerebrovascular history. Only one of these six patients had cerebral angiography and this was normal. Cerebral emboli were found at autopsy of another patient. Multiple intracerebral microthromboses were shown at autopsy in another patient.¹⁷

In animal experimentation, evidence has been accumulating that vasoactive substances such as 5-hydroxytryptamine, noradrenaline, and prostaglandins are involved in the pathogenesis of cerebral vasospasm.¹⁸ All of these substances have an ultimate effect of increasing the intracellular free calcium in the cerebrovascular smooth muscle cells.¹⁹ Calcium binds to troponin to initiate the actin-myosin coupling; and it has been shown that calcium is the final activator of the contractile protein in vascular smooth muscle.²⁰ Extracellular calcium is an absolute requirement for serotonin induced vascular spasm, and Allen et al²¹ showed varying degrees of spasm related to differing concentrations of the calcium environment.

It is of great interest that Edvinsson *et al*²² recently showed that nifedipine (a drug which selectively inhibits calcium influx) reduced the *in vitro* spasm of human pial arteries after its induction by 5-hydroxytryptamine, noradrenaline, and autologous blood or plasma.

Performance of cerebral arteriography in more patients with hypercalcaemia and focal neurological disturbances will establish whether arterial spasm is a chance or frequent association.

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