Letters


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Myasthenia gravis associated with a hormone producing malignant carcinoid tumour

Sir: Myasthenia gravis is often associated with thymic hyperplasia or thymoma,1 and an increased incidence of non-thymic malignancy has been reported.2 We describe a patient who developed myasthenia gravis 1 year after the diagnosis of a malignant carcinoid tumour had been made and 4 years after the onset of symptoms.

A 77-year-old retired insurance salesman was admitted to another hospital in March 1983 with acute urinary retention due to an enlarged prostate. Over the preceding 3 years the patient had complained of episodic diarrhoea, without the passage of blood or mucus, and accompanied by abdominal colic. He gave no history of flushing attacks or wheezing. Investigations over this period including sigmoidoscopy and barium enema examination were normal. A gastroscopy had demonstrated a small polyp which was removed and found to consist of hypertrophic gastric mucosa. The patient had undergone bilateral hernia repairs 15 years previously and a mastoid operation 10 years before that. Otherwise he had been well and took no medication. Transurethral resection of the prostate was performed, and histology showed benign prostatic hypertrophy. After operation he developed small bowel obstruction and a laparotomy was carried out. This revealed small bowel obstruction due to a tumour in the proximal ileum, with peritoneal seedlings and enlarged mesenteric lymph nodes, but no obvious liver involvement. Resection included 1 m of ischaemic small bowel with end to side jejun-ileal anastomosis. Histology of the resected tumour was characteristic of a mid-gut carcinoid tumour resulting in ischaemic mucosal necrosis of the small bowel. In both the bowel mucosa and mesenteric clumps of uniform tumour cells containing red granules staining positively with the diazonium technique were present.

Fourteen months later he was referred to this hospital because of progressive weakness in the trunk, neck, and limbs developing over several months. For 4 weeks prior to admission he had noticed ptosis, double vision, difficulty in chewing and swallowing. Examination showed bilateral ptosis, worse on the right, limitation of eye movements and diplopia in all directions, an inability to close his jaw fully and bilateral facial weakness. Weakness of his neck, trunk, and limb muscles was such that he was unable to stand or maintain his head in an upright position. These symptoms and signs were improved dramatically by an intravenous injection of edrophonium and treatment with pyridostigmine was started.

Investigations were as follows: haemoglobin 9.5 g/dl, a dimorphic blood film picture, serum iron 2.5 μmol/l, Total Iron Binding Capacity 72.6 μmol/l, % saturation 3-4%, positive faecal occult blood, serum B₁₂ 25 ng/l. A Schilling test showed reduced absorption of B₁₂ both with and without intrinsic factor. Urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion 205 μmol/24 h (normal less than 75 μmol/24 h), gamma GT 76 u/l (normal less than 50 u/l). Auto antibodies to striated muscle negative, to acetylcholine receptor 4-9 nmol/l (normal controls less than 0.2 nmol/l), and to gastric parietal cell weakly positive. Rapid Plasma Reagin Test and Total Iron Binding Capacity negative, a chest radiograph, isotope liver scan, urea and electrolytes, thyroid function tests, serum folate, serum aldolase and creatine kinase all normal. Electrophysiological studies showed normal motor and sensory conduction in the right median nerve. With repetitive stimulation of the right ulnar nerve at the wrist recording from right adductor digiti minimi showed initial response with amplitude 11·2 mV and classical myasthenic decrement at stimulation rates from 1–10/Hz. The decrement of the 4th response was as follows; 1/Hz 10·5%, 2/Hz 39·3%, 3/Hz 39·3%, 5/Hz 28·3%, 10/Hz 24·7%. Stimulating at 50Hz for 128 stimuli produced a small increment of the second response and then a progressive decrement to under 50% of the initial amplitude. Microscopic examination of muscle obtained at biopsy of palmarus longus showed variation in size of muscle fibres which were generally slightly smaller than normal. There was no significant small fibre grouping, no lymphorrhages and no inflammation. Histochecmy showed no fibre type preponderance, degeneration, nor fibre type grouping. Methylene blue staining of motor end plates showed elongation and branching of terminal expansions compatible with myasthenia gravis.

The patient’s anaemia was treated initially with oral iron and parenteral hydroxyecobalamin. Prednisolone and azathioprine were started; his condition improved gradually over the next 2 months and he was able to leave hospital 11 weeks after admission.

Myasthenia gravis is associated with a higher than expected incidence of non-thymic malignancy. A retrospective study of 1243 patients with myasthenia gravis revealed 94 non-thymic cancers, most commonly affecting breast, lung, colon and rectum.2 In particular the incidence of malignancy within 2 years of the diagnosis of myasthenia gravis was much greater than expected. Thymic disorders remain the most consistently recognised abnormalities associated with myasthenia, thymic germinal centres or hyperplasia being present in 65% of cases and a further 10% having a thymoma.1 Thymic carcinoid should be differentiated from thymoma, having a significant malignant potential, being associated with Cushings syndrome, and occurring with multiple endocrine adenomatosis.5 Features of the carcinoid syndrome occur in about 10% of carcinoid tumours, usually those in the jejunum and ileum.6 Systemic symptoms, usually attacks of diarrhoea, abdominal colic, flushing, or wheezing are due to the production of a variety of secretory products, most often 5-hydroxytryptamine (5-HT) and kinins. A proximal myopathy in some patients with the carcinoid syndrome has been attributed to excess 5-HT,3 and thus treated with cyproheptadine.

The patient we describe complained of attacks of diarrhoea and abdominal colic for 3 years before the diagnosis of a carcinoid tumour became evident after laparotomy, when an excess urinary excretion of 5-HIAA was demonstrated. Just over 1 year later he developed myasthenia gravis. He did not have a carcinoid myopathy and muscle biopsy changes were compatible with myasthenia gravis. When myasthenia gravis develops in association with a malignant tumour weakness may be wrongly attributed to the malignancy or general debility, the diagnosis missed, and the patient denied effective treatment for his condition.
We are grateful to Dr DW Day for the pathological report on the tumour, Dr PH Buxton for the muscle biopsy, Professor JM Newsom-Davis for the acetylcholine receptor antibody assay, and Dr M Hayward for the electrophysiological studies.

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Multiple adverse reactions following metrizamide myelography

Sir: Metrizamide, a nonionic contrast medium, is still widely used for routine myelography and cisternography although there are now other agents such as iohexol with fewer complications and less expense.1 There are several reports based on human and animal observations concerning metrizamide’s adverse reactions;2–5 however, from the work of Killebrew et al6 it appears that there may still be side effects which have not yet been adequately emphasised. We report a patient with a mild cervical cord lesion who developed generalised convulsions, neurobehavioural disturbances and persistent myelopathy following metrizamide lumbar myelography.

A 50-year-old farmer was admitted with a history of having woken up 15 days earlier complaining of numbness, pins and needles in the arms and legs and mild difficulty in using both upper and lower limbs, without any bladder dysfunction. He had been well the day before and there was no relevant past history. On examination he had mild pyramidal signs in all four limbs consisting of increased tendon reflexes, sustained ankle clonus on the right and unsustained on the left, mild difficulty in fine movements of both hands without any detectable weakness in the muscles and equivocal plantar reflexes. The cranial nerves were intact, the abdominal reflexes were present, there were no cerebellar signs or objective sensory disturbances. Normal laboratory data, included blood count, erythrocyte sedimentation rate, blood urea and electrolytes, VDR, serum B12, urine analysis, ECG, chest radiographs, computed brain tomography and CSF obtained during myelography. Blood sugar was slightly increased and the glucose tolerance test showed mild diabetes mellitus. Plain cervical radiographs showed degenerative changes and small posterior osteophytes between C2–C3 and C3–C4.

The patient’s symptoms and signs remained unchanged for the following three weeks. Then lumbar myelography was carried out. Three g (0.33 g/ml) of metrizamide were administered. This showed narrowing of the spinal canal in the cervical region and indentation of the contrast medium at the level C2-C3 and C3-C4 due to posterior osteophytes. The contrast medium passed freely through the cervical canal. During the investigation there was intracranial spill of the contrast medium with high concentration of metrizamide in the posterior fossa. Twenty minutes later the patient had severe generalised convulsions. He was treated with intravenous diazepam, phenytoin and steroids and in the next few hours he had three more generalised seizures with an hour interval between. For the following 24 hours he was severely confused and gradually by the end of 48 hours he recovered. The next morning following the myelogram he was found to have considerable deterioration of his spastic tetraparesis with urinary retention and he was catheterised for a few days. He had moderate to severe weakness of shoulder girdle muscles which gradually became atrophic with widespread and frequent fasciculations. He also had a sensory level to pin-prick at C4. The patient refused at that time to undergo a cervical laminectomy. Although his clinical state remained unchanged, a decompressive cervical laminectomy at C3–C4 and C4–C5 level was carried out 3 months later in another hospital. Seven months later the patient’s clinical condition has not changed.

Headache, nausea and vomiting are fairly frequent side effects following metrizamide myelography. Other less common adverse reactions include seizures, diplopia, menigism, fever, neuro-behavioural disorders (hallucinations, confusion, anxiety and disorientation) and EEG changes.7–10 Lower extremity myoclonus has been reported as a very rare complication.11 All adverse reactions of metrizamide have been reversible and usually do not last longer than a few days. Metrizamide’s adverse reactions are probably due to meningeal-neuronal cerebral and spinal irritation and it has been shown that metrizamide penetrates the brain substance.12 There may be several explanations for our patient’s sudden deterioration of cervical myelopathy. The sudden onset of the spinal symptoms in addition to the normal CSF suggests probably a vascular mechanism. Demyelination is rather unlikely as there have been no previous episodes and the patient was over 50 years of age. Deterioration due to the lumbar puncture itself on myelography was not possible as the cervical spondylosis was not severe and there was no spinal block. The patient’s sudden deterioration may have been caused by a vascular accident at myelography, or during the generalised convolution; on the other hand myelopathy due to metrizamide cannot be excluded and could be the possible explanation particularly in a patient apparently sensitive to metrizamide. All the reported metrizamide’s adverse reactions due to toxic encephalopathy are reversible within a few days. Reports of cases with spinal irritation or myelopathy due to metrizamide are very rare and it is possible that this reaction may last much longer.13–15

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