Self-assessment questions

Reversible confusional state in an elderly man

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A 76-year-old man was noted by his sister, with whom he lived, to have become increasingly confused for 6 months. He gradually became more dependent on her, even for basic activities of daily living such as dressing, but he remained fully ambulant and was not unsteady. He had no headaches or other specific symptoms, there was no relevant medical history, and he was not receiving any regular medications.

When referred to hospital he was disorientated in time and place. His gait was normal, there was no evidence of cranial nerve or limb deficit. His visual fields and fundal examination were normal, and there were no cardiorespiratory or other abnormalities on physical examination. Full blood count, erythrocyte sedimentation rate, renal and liver function tests were normal, as were thyroid-stimulating hormone (TSH), vitamin B12 and blood glucose levels. Chest X-ray and electrocardiogram were unremarkable. Computed tomography (CT) of the brain suggested a cause for the confusional state which was confirmed by magnetic resonance imaging (MRI) of the brain (figures 1 and 2).

Figure 1 T1-weighted MRI scan (coronal section)

Figure 2 MRI scan of the brain (sagittal section)

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Accepted 3 December 1998

Questions

- 1 List the causes of acute confusional state.
- 2 What do the MRI scans show?
- 3 Which blood test would confirm the diagnosis?
- 4 What specific medical treatment should the patient receive?

Answers

QUESTION 1

Acute confusional state is the term most commonly used by British psychiatrists. Synonyms include acute psycho-organic syndrome, acute organic reaction, acute brain syndrome and delirium. Lipowski¹ defines this state (which he prefers to the name delirium) as an episode of acute onset and transient duration, characterised by global cognitive impairment, and due to widespread disturbance of cerebral metabolism. The very young and the aged are particularly prone to acute confusional states.

There is a framework for tracing the cause of acute confusional states (see box).²

QUESTION 2

CT scan of the brain showed no intracerebral abnormality and no significant degree of intracerebral atrophy, but there was marked expansion of the pituitary fossa (4 × 4 cm) with destruction of the walls. T1-weighted MRI (figures) confirmed a large pituitary tumour in an expanded sella with lateral extension and destruction of the posterior clinoid and clivus, but no evidence of suprasellar extension.

QUESTION 3

Measurement of serum prolactin would confirm the diagnosis. In our patient serum prolactin was extremely high at 33 884 mU/l, consistent with prolactinoma (normal level 45–375 mU/l). Basal adrenocorticotropin and serum cortisol levels were normal, with a subnormal synacthen test (basal cortisol 308 nmol/l which increased to 503 nmol/l 30 min after intramuscular injection of 250 µg Synacthen. A normal response should produce a rise in cortisol to 550 nmol/l after 30 min). Free thyroxine and TSH were normal. Follicle-stimulating hormone was low at 2.7 IU/l, and luteinising hormone low at 0.8 IU/l, with a low testosterone level of 2.0 nmol/l and normal growth hormone level.

QUESTION 4

A diagnosis of megaprolactinoma was made and he was commenced on cabergoline 0.5 mg twice weekly.

Discussion

To the best of our knowledge this is the oldest individual to be reported with pituitary macroprolactinoma. Our patient improved remarkably with resolution of his confusional state, his serum prolactin level fell to 3373 mU/l within 2

Causes of acute confusional state

Intracranial

- space-occupying lesion, eg, tumour
- trauma, ie, concussion
- infections, eg, meningitis
- cerebrovascular accidents
- epilepsy

Extracranial

- infections, eg, pneumonia
- metabolic, eg, liver failure
- anoxic, eg, cardiac or respiratory failure
- vascular, eg, giant cell arteritis
- endocrine, eg, hypoglycaemia
- vitamin deficiency, eg, thiamine
- intoxication / withdrawal of alcohol or drugs
- psychological / environmental
- other, eg, hypothermia

weeks, with normalisation of the hormonal profile, including serum prolactin, after 3 months.

Pituitary tumours in the elderly often present with non-specific symptoms and the diagnosis is commonly missed.³ The majority of large prolactinomas in men are due to rapidly growing tumours which are often invasive and bromocriptine-resistant.⁴ Prolactinomas in women commonly present as small intrasellar tumours.⁵

Treatment with the semisynthetic ergot alkaloid bromocriptine, an orally active dopamine agonist, introduced in 1971 for the treatment of hyperprolactinaemia and prolactinomas, may be beneficial, with correction of visual field defects and reduction or disappearance of the adenoma. Cabergoline is a long-acting dopamine agonist specific for D2 receptors and is effective in normalising serum prolactin level in patients with macroprolactinoma.⁶ Cabergoline may be preferable to bromocriptine because of its effectiveness, low side-effect profile, and being long acting (can be given once a week). Medical treatment with a dopaminergic agonist is the preferred mode of treatment for macroprolactinoma, and surgical excision is only recommended when the tumour is life threatening.

Final diagnosis

Megaprolactinoma.

Keywords: confusional state; macroprolactinoma; cabergoline

1 Jones R, Arie T. The acutely confused patient. In: Exton-Smith AN, Weksler ME, eds, *Practical geriatric medicine*. London, Churchill Livingstone, 1985; pp 100–1.

2 Abbas M, Carter J, Osagie A, Levy R. Hypophyseal insufficiency in old age: a forgotten syndrome? *Age Ageing* 1998;27:251–6.

3 Turner HE, Wass JA. Pituitary tumours in the elderly (review of 84 references). *Baillieres Clin Endocrinol Metab* 1997;11:407–22.

4 Delgrange E, Trouillas J. Sex related difference in the growth of prolactinomas; a clinical and proliferation marker study. *J Clin Endocrinol Metab* 1997;82:102–7.

5 Colao A, Di Sarno A. Long-term and low-dose treatment of cabergoline induces macroprolactinoma shrinkage. *J Clin Endocrinol Metab* 1997;82:3574–9.

6 Berezin M, Shimon I. Prolactinoma in 53 men; clinical characteristics and mode of treatment (male prolactinoma). *J Endocrinol Invest* 1995;18:436–41.

A mentally retarded man with a nasal discharge

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A 35-year-old mentally retarded Chinese man presented with a 6 month history of intermittent, foul-smelling nasal discharge from his left nostril. He had been treated with antibiotics, topical nasal decongestants and steroid nasal sprays without success, and plain sinus X-rays had shown an opaque left maxillary antrum. Because of this a left antral wash-out had been performed on two occasions, followed by an inferior meatal antrostomy, but still without resolution of his symptoms. His medical history included glaucoma affecting the left eye for which he had undergone surgery, and a history of grand-mal epilepsy treated with anticonvulsants. Examination revealed port-wine naevi over his left frontal and malar regions, and hypertrophy of the frontal and maxillary bone on the left. Purulent secretions were present in the left nasal cavity. The nasal mucosa was congested but no polyps, foreign bodies or other obstructive lesions were seen. Neurological examination revealed a reduction of the motor power of his right arm and leg to grade 4/6. In view of his persistent nasal symptoms, a computed tomography (CT) scan of the paranasal sinuses was performed (figures 1–3).

Figure 1 Axial contrast CT brain scan

Figure 2 Axial contrast CT brain scan

Figure 3 Coronal non-contrast CT brain scan

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Questions

- 1 List the radiological abnormalities visible on the CT scans.
- 2 What is the most likely congenital syndrome that this man is suffering from and what is the differential diagnosis?
- 3 What is the most likely diagnosis of his nasal problem and what is the treatment?

Answers

QUESTION 1

Figure 1 shows cerebral atrophy and, tram-line cortical calcification of the left occipital region. Figure 2 shows hypertrophy of the left choroid plexus in the left ventricle, and tram-line calcification in the left occipital and the parietal region of the brain cortex. On the coronal non-contrast CT scan (figure 3), mucosal thickening of the left maxillary sinus, hypertrophy of the frontal and maxillary sinuses, a prominent frontal diploic bone, and evidence of previous left inferior meatal antrostomy can be seen.

QUESTION 2

The diagnosis is encephalotrigeminal angiomas (Sturge-Weber syndrome). The differential diagnosis includes Wyburn-Mason syndrome and leukodystrophy with meningeal angiomas.

QUESTION 3

This patient has been suffering from chronic maxillary sinusitis. As conservative treatment by antibiotics and steroids had failed and the symptoms recurred after antral wash-out, functional endoscopic sinus surgery is indicated. A middle meatal antrostomy is required under endoscopic guidance. This improves ventilation and restores normal mucociliary clearance towards the natural ostium of the maxillary sinus.

Discussion

This patient was diagnosed as having encephalotrigeminal angiomas (Sturge-Weber syndrome) during childhood. It is a non-hereditary condition that includes a port-wine capillary naevus on the face and is often in the distribution of the first division of the trigeminal nerve. These patients may also have convulsions which are focal and involve the contralateral side of the body. Contralateral hemiparesis and mental retardation may be present. Occasionally homonymous hemianopia is reported. Ipsilateral intracranial calcifications are found on plain skull X-ray. These calcifications are characteristically in paired lines, termed 'tram-line' calcification. Increased intra-ocular pressure may be caused by angiomatous involvement of the uveal tract and thus can give rise to enlargement of the involved globe. About two-thirds of patients with this condition have epilepsy. There is great variability in the severity of the individual symptoms, and one or more may be missing entirely. Haemangiomas may be found in parts of the body other than the face, but rarely in the fundi. These may be extensive and associated with hypertrophy of the limbs and deep varices.

The intracranial lesion is a capillary haemangioma that involves the meninges in the area supplied by the first division of the trigeminal nerve. It is related to the superficial vessels occupying the sulci over the convexity, particularly in the occipital and parietal regions. Such haemangiomas may cause atrophy of the underlying brain tissue. Degenerative changes in cerebral tissue just below the gyral surface cause

the characteristic calcifications which are limited to the convexity of the brain. The characteristic gyral pattern is almost pathognomonic of this condition.

Radiological diagnosis of Sturge-Weber syndrome is based on the recognition of the characteristic 'tram-line' calcifications on plain skull X-ray. However, CT scanning makes it possible to identify the classical signs of Sturge-Weber syndrome earlier and more clearly than on a plain X-ray, by allowing early recognition of small intracranial calcifications, cerebral atrophy, unilateral shrinkage of the cranium, hypertrophy of diploic bone or paranasal sinus hypertrophy. Moreover, anomalies of vasculature such as pial angiomas or choroid plexus hypertrophy which have only been identifiable on angiography in the past¹ can be demonstrated clearly on a CT scan. More recently, magnetic resonance imaging has been found to be more efficient in making the diagnosis and detecting lesions related to the clinical neurological status of the patient.²

Therapy is symptomatic, although early surgical excision in the form of lobectomy and hemispherectomy is sometime done in the hope of preventing seizures that may be difficult to control and associated with intellectual decline.³ The treatment option for chronic maxillary sinusitis is either medical or surgical.⁴ Once a dental cause for the unilateral maxillary sinusitis has been excluded, a minimum course of 10 days of broad-spectrum oral antibiotics which covers both aerobic and anaerobic infection should be given. The addition of a short course of topical nasal steroids may help to reduce mucosal swelling around the sinus orifice and regain mucociliary clearance of the sinus. If conservative treatment fails, a sinus washout can be performed after 3 to 4 weeks to clear the mucus collected in the sinus. Pus is thus obtained from the sinus for culture and sensitivity which help to guide the antibiotic treatment. More than one antral washout may be required before symptoms can effectively be alleviated. However, if the above means fail to control symptoms, a sinus-drainage operation is required. In the past, inferior meatal antrostomy and the 'Caldwell-Luc' operation were the mainstays of surgical treatment for chronic maxillary sinusitis. These aimed to restore the ventilation, allow free drainage of secretions by gravity and eradicate diseased mucosa in the antrum. Recent research on chronic sinusitis has stressed the importance of the ethmoid-middle meatal complex, an area where the mucociliary clearance of secretions from the frontal, ethmoid and maxillary sinuses may be obstructed. Functional endoscopic sinus surgery (FESS), based on logical physiological concepts, has addressed these underlying problems by aiming to restore ventilation and mucociliary clearance of the paranasal sinuses.⁵ Using rigid endoscopes of different viewing angles (0°, 30° and 70°), allows excellent visualisation of the hidden areas within the nasal cavities and paranasal sinuses. FESS is less traumatic than traditional surgery and requires shorter duration of hospitalisation.

Final diagnosis

Encephalotrigeminal angiomas (Sturge-Weber syndrome).

Keywords: encephalotrigeminal angiomas; Sturge-Weber syndrome; nasal discharge

- 1 Fötter R, Sager WD, Schneider GH, *et al.* Computer tomography in the Sturge-Weber syndrome. *Computertomographie* 1981;1:80-2.
- 2 Marti-Bonmati L, Menor F, Mulas F. The Sturge-Weber syndrome: correlation between the clinical status and radiological CT and MRI findings. *Childs Nerv Syst* 1993;9:107-9.
- 3 Holmes GL. Surgery for intractable seizures in infancy and early children. *Neurology* 1993;43:S28-S37.
- 4 Mackay I. Infective rhinitis and sinusitis. In: *Scott-Brown's Otolaryngology*, 6th edn, vol 3. Butterworths, London, 1997; pp 810-35.
- 5 Stammberger H. Endoscopic endonasal sinus surgery. Concept in treating of recurrent rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. *Otolaryngol Head Neck Surg* 1986;94:143-7.

Sudden-onset watery diarrhoea in a middle-aged woman

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A 55-year-old woman presented with a 2-month history of profuse watery diarrhoea. The onset of diarrhoea was very sudden – she was woken up at 04.00 h one morning with a severe urge to move her bowels. The motions were watery, frequency averaging five times per day. There was no rectal bleeding, abdominal pain or vomiting. She had lost 2 kg in weight but there was no history of iritis, arthritis, rashes or aphthous ulcers. Clinical examination was unremarkable. Laboratory investigations revealed normal full blood count, urea and electrolytes. C-Reactive protein was not raised and there was no growth on stool culture. Colonoscopy showed mild erythema with loss of vascular pattern in the transverse colon, but no ulceration. Multiple biopsies were taken from the region. Histology of the colonic biopsy is shown in the figure.

Figure Histology of the colonic biopsy

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Questions

- 1 What is the diagnosis?
- 2 What is the pathogenesis of this condition?

Answers

QUESTION 1

The diagnosis is collagenous colitis. Histologically, there is a characteristic, thick, subepithelial collagen band. There is a chronic inflammatory cell infiltration of the lamina propria, but the crypt architecture is well maintained.

QUESTION 2

It has been postulated that an initial insult by a luminal agent, which may be an infective agent, gluten, or a drug, eg, a non-steroidal anti-inflammatory, may damage the bowel mucosa leading to an autoimmune response, with ongoing chronic inflammation in susceptible individuals.¹

Discussion

Collagenous colitis was first described by Lindstrom in 1976.² He reported a patient with chronic watery diarrhoea in whom a subepithelial collagen band was seen on rectal biopsy. More recent reports of collagenous colitis have suggested that it is not as rare as initially supposed.³⁻⁶ There is another group of patients with colorectal biopsies revealing changes very similar to collagenous colitis in terms of lymphocytic inflammation, but without a collagen band. To reduce confusion the term 'lymphocytic colitis' has been suggested to describe this entity. 'Microscopic colitis', in turn, is a general term denoting conditions characterised by microscopic colonic inflammation, which includes the subsets of collagenous and lymphocytic colitis.¹

Collagenous colitis has a striking female predominance (10:1) and the mean age is in the sixth decade.¹ There is chronic, watery diarrhoea with no bleeding. The diarrhoea is secretory in nature, with an active colonic secretion of chloride ions associated with a passive secretion of sodium and water. The diarrhoea may be of sudden onset in over 40% of patients.³ Typically, colonoscopy is normal or shows only mild, nonspecific changes. All the other investigations are negative and diagnosis depends on histology. There is an increased prevalence of collagen deposition in the proximal colon. In an initial series, up to 40% of cases were reported to have normal histology of the rectosigmoid colon.⁴ This has been challenged in a recent study which found that left-sided biopsies alone would have been sufficient for diagnosis in 89% of cases.⁵ The collagen band consists of type III collagen rather than the usual type IV. Since type III is usually involved in repair processes, the suggestion is

Features of collagenous colitis

- watery diarrhoea with no bleeding
- female preponderance (F:M, 10:1)
- mean age: sixth decade (rare in children)
- colonoscopy normal or only minor non-specific changes
- histology diagnostic: subepithelial collagen band in colonic biopsy
- treatment largely symptomatic
- chronic relapsing course (spontaneous remission in about 1/3 rd)

that the collagen band is a result of inflammation. This view is supported by the results of sequential biopsy studies showing inflammation preceding the appearance of collagen.⁴ Most evidence suggests that the band is not important in the pathophysiology of the disease. The presence or thickness of the collagen band correlates poorly with the symptoms, whereas the degree of inflammation correlates with diarrhoea and response to treatment.⁴ Certain disease associations have been noted in patients with collagenous colitis. These include ulcerative colitis, Crohn's disease, coeliac disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, pernicious anaemia, myasthenia gravis and Hashimoto's disease.³

The natural history of collagenous colitis appears to be benign, following a chronic relapsing course. Often spontaneous or treatment induced, sustained resolution of symptoms may occur. The collagen band can disappear during therapy or occasionally in association with spontaneous remission. Sulphasalazine and other 5-ASA derivatives have the best response rate.¹ Steroids are also very effective, but their response is not sustained after withdrawal and the doses required are often high.³ Symptomatic treatment with anti-diarrhoeals is the only therapy required in most cases. Surgery in the form of ileostomy for faecal diversion may be required in patients with incapacitating, unresponsive disease.⁶ Our patient responded very well to a short course of steroids. Her diarrhoea settled within a few days of starting prednisolone and uncharacteristically she remained in sustained remission months after stopping the steroids.

Final diagnosis

Collagenous colitis.

Keywords: collagenous colitis; microscopic colitis

1 Jawhari A, Talbot IC. Microscopic, lymphocytic and collagenous colitis. *Histopathology* 1996;**29**:101-10.

2 Lindstrom C. Collagenous colitis with watery diarrhoea: a new entity? *Pathol Eur* 1976;**11**:87-9.

3 Bohr J, Tysk C, Eriksson S, *et al*. Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients. *Gut* 1996;**39**:846-51.

4 Carpenter HA, Tremaine WJ, Batts KP, *et al*. Sequential histologic evaluations in collagenous colitis. Correlations

with disease behaviour and sampling strategy. *Dig Dis Sci* 1992;**37**:1903-9.

5 Goff JS, Barnett JL, Pelke T, *et al*. Collagenous colitis: histopathology and clinical course. *Am J Gastroenterol* 1997;**92**: 57-60.

6 Jarnerot G, Tysk C, Bohr J, *et al*. Collagenous colitis and fecal stream diversion. *Gastroenterology* 1995;**109**:449-55.

Pancreatitis and chronic abdominal pain in a patient with AIDS

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A 37-year-old white woman was infected with the human immunodeficiency virus (HIV) through a blood transfusion which she received during a complicated labour in the Ivory Coast. Three years later, due to a decline in the CD4⁺ cell counts to 200/ml, zidovudine (AZT) and trimethoprim-cotrimoxazole were administered. A few months later, zalcitabine (ddC) was added, due to the appearance of fever, abdominal pain and weight loss, and a further decline in the CD4⁺ cell counts down to 15/ml. Despite these measures the patient continued to complain of abdominal pain, which was often exacerbated by food intake. Laboratory studies then showed normal serum amylase and liver enzyme levels. Abdominal ultrasonography (US) and gastroscopy were normal. Due to a suspected role of the antiretroviral drug therapy in inducing the abdominal pain, AZT and ddC were discontinued.

Three months later, the patient was admitted because of severe abdominal pain, vomiting and a fever of 38.5°C. On examination, marked epigastric tenderness was noted. Investigation results were as follows: amylase 1120 IU/l, hypocalcaemia (1.52 mmol/l), alkaline phosphate 219 IU/l, and gamma-glutamyl transpeptidase 478 IU/l. US and computed tomography (CT) revealed gall bladder wall thickening, with a dilated common bile duct and no evidence of stones. The pancreas was mildly enlarged and oedematous.

A diagnosis of pancreatitis was made, a nasogastric tube was inserted and fluids were administered with marked improvement. Blood and urine cultures for cytomegalovirus (CMV) were negative, and fundoscopic examination did not reveal the presence of CMV retinitis. Blood cultures were negative for *Mycobacterium avium-intracellulare* (MAI), and *Cryptococcus neformans* antigens were not detected.

A few weeks later, epigastric pain recurred. Amylase levels remained normal. An endoscopic retrograde cholangiopancreatography (ERCP) was performed (figure). Brush cultures from the mucosa and the biliary fluid grew CMV. Ganciclovir was administered at a dose of 10 mg/kg daily for 3 weeks, followed by 5 mg/kg daily, with improvement in her general condition and a gradual decrease of the pain.

Three months later, parenteral nutrition was started due to intractable abdominal pain which was related to food intake. On this therapy the patient developed severe abdominal pain accompanied by deterioration of liver function tests. A repeat ERCP was performed.

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Figure ERCP with contrast material within the common bile duct, showing mild dilatation without any filling defects. There was no dilatation of the pancreatic duct

Questions

- 1 What diagnosis is suggested by the findings on ERCP?
- 2 Which other organism besides CMV is likely to be found in the biliary tract in this patient?
- 3 What is the optimal management of this patient's condition?

Answers

QUESTION 1

The initial ERCP revealed marked diffuse inflammation around the area of the papilla of Vater, biliary tract narrowing with mild dilatation of the common bile duct without dilatation of the pancreatic duct. The changes in the biliary ducts were consistent with acquired immune deficiency syndrome (AIDS). Biopsies taken from the duodenal mucosa and the papilla of Vater during papillotomy, revealed a lymphocytic infiltration with inclusion bodies which reacted to monoclonal antibodies specific to CMV. The repeat ERCP showed, again, a dilated common bile duct with irregular borders with no filling defects. The papilla of Vater was draining bile adequately and the pancreatic duct appeared normal. Papillotomy was repeated. CMV inclusion bodies could not be found.

QUESTION 2

Histologic examination of the small intestine mucosa from the repeated ERCP, revealed *Cryptosporidium*. Both CMV and *Cryptosporidium* have been found, often simultaneously, within the biliary epithelium of patients with AIDS cholangiopathy. However, their role in the pathogenesis of this cholangiopathy has not been well defined. Azithromycin and oral narcotics were administered with mild improvement. Six weeks later the patient was hospitalized again due to high fever. *Candida albicans* grew in blood culture, and amphotericin B therapy was initiated. The patient died few days later.

QUESTION 3

AIDS cholangiopathy is best treated by sphincterotomy or surgical drainage of the common bile duct. This is the most effective method that leads to a rapid relief of pain which may last. Although it is legitimate to attempt eradicating any pathogens found within the biliary epithelia such as CMV or *Cryptosporidium*, these actions do not seem to affect the general biliary process or the outcome of these patients, as the primary pathological process is not affected.

Discussion

We have described an HIV-positive patient who presented with CMV-related acute pancreatitis, as the initial manifestation of AIDS cholangiopathy. AIDS-related cholangiopathy is a well described entity which presents in advanced stages of AIDS. CMV and *Cryptosporidium* are frequently found within the biliary epithelium, although their role in inducing AIDS cholangiopathy is not clear.

Pancreatitis occurs in about 5% of HIV-infected individuals,¹ and is mostly related to drugs, such as dideoxyinosine (ddI), zalcitabine (ddC), pentamidine, and trimethoprim-sulfamethoxazole.² In addition to common aetiologies of acute pancreatitis, such as chole-

Learning points

- sclerosing cholangitis may be the only manifestation of AIDS
- CMV infection plays a limited role in the induction and propagation of AIDS cholangiopathy
- acute pancreatitis can be a presenting symptom of AIDS cholangiopathy
- endoscopic sphincterotomy relieves the patient's symptoms; however, it does not change the outcome of AIDS cholangiopathy

lithiasis and alcoholism, opportunistic pathogens such as CMV, *Cryptococcus neoformans* and *Toxoplasma gondii*³ are also important causes of pancreatitis in patients with HIV infection. CMV infection is very common in advanced stages of AIDS. The gastrointestinal tract is the most involved organ in CMV infection, except for the retina.⁴ Autopsy studies have shown that CMV is the most common pathogen that involves the pancreas in AIDS patients.⁵ Antemortem diagnosis of CMV pancreatitis requires a high index of suspicion, and may be achieved by demonstrating inclusion bodies within the pancreatic parenchyma and viral culture of the pancreatic tissue. Epithelial cells from the ampulla of Vater harbouring CMV inclusion bodies, suggests strongly that CMV was the causative agent of pancreatitis in our patient.⁶

Despite the eradication of CMV from the pancreas, our patient continued to suffer from intermittent abdominal pain with cholestasis, typical of AIDS cholangiopathy.⁷ Usually, patients with AIDS cholangiopathy are well advanced in their disease, with CD4 counts below 100/ml. AIDS cholangiopathy comprises biliary tract narrowing, which may be either a result of papillary stenosis, sclerosing cholangitis, or a combination of the two processes, and is well recognized by ERCP.⁸ CMV and *Cryptosporidium* are common, and the presence of MAI has also been reported.⁷ Treatment to eradicate CMV may contribute to improvement in the patient's condition.⁷ With the lack of diarrhoea and signs of malabsorption, *Cryptosporidium* was unlikely to have played a significant role in causing the patient's symptoms.

Despite the suggested role of CMV in the pathogenesis of AIDS cholangiopathy, eradication of CMV does not seem to change the outcome or the long-term prognosis, probably because of the advanced stage of their HIV infection.

Final diagnosis

AIDS cholangiopathy.

Keywords: AIDS cholangiopathy; pancreatitis; cytomegalovirus; cryptosporidium

- 1 Kahn J. Anti-human immunodeficiency virus therapeutics: now and the future. *Semin Liver Dis* 1992;12:121-7.
- 2 Cappell MS, Marks M. Acute pancreatitis in HIV-seropositive patients: a case control study of 44 patients. *Am J Med* 1995;98:243-8.
- 3 Dowell SF, Murre W, Hutchins GM. The spectrum of pancreatic pathology in patients with AIDS. *Mod Pathol* 1990;3:49-53.
- 4 Jacobson MA, O'Donnell JJ, Porteous D, Bordie HR, Feigal D, Mills J. Retinal and gastrointestinal disease due to cytomegalovirus in patients with the acquired immune deficiency syndrome: prevalence, natural history, and response to ganciclovir therapy. *Q J Med* 1988;67:473-86.
- 5 Niedt GW, Schinella RA. Acquired immunodeficiency syndrome. Clinicopathologic study of 56 autopsies. *Arch Pathol Lab Med* 1985;109:727-34.
- 6 Cella P, Gupta S. Diagnosis of pancreatitis in AIDS by endoscopic retrograde cholangiopancreatography (letter). *N Engl J Med* 1992;326:204; correction 844.
- 7 Cello JP. Acquired immunodeficiency syndrome cholangiopathy: spectrum of disease. *Am J Med* 1989;86:539-46.
- 8 Cello JP, Chan MF. Long-term follow-up of endoscopic retrograde cholangiopancreatography sphincterotomy for patients with acquired immune deficiency syndrome papillary stenosis. *Am J Med* 1995;99:600-3.

Dysphagia and hypercalcaemia

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A 68-year-old man presented with a 3-month history of progressive dysphagia, anorexia, weight loss, fatigue and malaise. Two years previously, he had received palliative radiotherapy for squamous cell carcinoma of the right bronchus. There was no medical history of gastrointestinal disease and, apart from difficulty swallowing, the patient did not complain of any other gastrointestinal symptoms, urinary symptoms, or visual disturbance. On examination, the patient was alert, but cachectic. There were no signs of cognitive impairment. There was no palpable lymphadenopathy or other mass in the neck. Examination of the mouth and pharynx revealed no abnormalities. Respiratory examination revealed collapse of the right lower lobe. Abdominal examination revealed a hard, irregular, non-tender, non-pulsatile liver edge, palpable 4 cm below the right costal margin. There were no signs of chronic liver disease. Rectal, cardiovascular and neurological examinations were normal. Investigations showed haemoglobin 10.3 g/dl, mean corpuscular volume 78.2 fl, total white blood cell count $8.45 \times 10^9/l$ (normal differential count) and erythrocyte sedimentation rate 91 mm in the first hour. Renal and thyroid function were normal. Random blood glucose was 6.3 mmol/l. Alkaline phosphatase 487 IU/l (normal range 70-250 IU/l), serum calcium 3.71 mmol/l, serum phosphate 1.17 mmol/l (0.75-1.40 mmol/l) and serum albumin 25 g/l (34-48 g/l). Corrected serum calcium was 4.01 mmol/l (2.22-2.56 mmol/l). Other liver function tests were normal. Serum parathyroid hormone, as measured by radio-immunoassay, was 80 ng/l (< 100 ng/l) and angiotensin-converting enzyme levels were normal. Chest X-ray confirmed collapse of the right lower lobe, due to a carcinoma obstructing the right bronchus. Abdominal ultrasound showed multiple small echogenic lesions throughout the liver, consistent with metastatic deposits from the bronchial carcinoma. An electrocardiogram was normal. An oesophago-gastro-duodenoscopy was normal. In particular, there was no evidence of extrinsic oesophageal compression or oesophageal infiltration by the bronchial carcinoma.

Questions

- 1 What is the cause of dysphagia?
- 2 What other clinical features may be present?

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Accepted 3 December 1998

Answers

QUESTION 1

The absence of a mechanical obstruction suggests a neuromuscular cause for dysphagia. In this patient, the cause of dysphagia was hypercalcaemia. He was treated with intravenous normal saline (3 l/24 h) and 30 mg of intravenous pamidronate disodium. Two days later, corrected serum calcium had fallen to 3.22 mmol/l. Five days after admission, his swallowing began to improve and on day six, corrected serum calcium was 2.62 mmol/l. His serum calcium normalised on day eight, (2.48 mmol/l), and on day nine he was able to swallow normally.

QUESTION 2

The other clinical features of hypercalcaemia are given in the box.

Discussion

Hypercalcaemia has several recognised effects on the gastrointestinal system, but dysphagia has rarely been reported.¹ Our patient had hypercalcaemia due to metastatic carcinoma of the bronchus. Carcinoma of the bronchus can cause dysphagia due to extrinsic compression or malignant invasion of the oesophagus, but, in this case, no such pathology was found. The rapid improvement in our patient's dysphagia following normalisation of serum calcium levels suggests a causal relationship.

Calcium ions are involved in neuromuscular transmission and muscular contractions. At the neuromuscular junction, release of acetylcholine is stimulated by the rapid influx of calcium ions into the synapse. At the muscular level, rises in intracellular calcium levels stimulate muscular contractions. This occurs in all muscle types. In skeletal muscle, rises in intracellular calcium stimulate interaction between actin and myosin, by removing the inhibitory influence of the troponin-tropomyosin complex. In smooth muscle, calcium ions bind to calmodulin which, via activation of a protein kinase, phosphorylates myosin. This phosphorylation is a pre-requisite for activation of the actin-myosin complex, which leads to muscular contraction. The contractile process of cardiac muscle is similar to that of skeletal muscle.

When serum calcium levels fall, tetany is a recognised sign. This reflects hyperexcitability of the nervous system. This occurs because, as calcium levels fall, neuronal membranes become increasingly permeable to sodium ions, allowing easier propagation of action potentials. Conversely, hypercalcaemia leads to depression of the nervous system. In the gastrointestinal system, this leads to reduced

Clinical features of hypercalcaemia

General

- fatigue
- weight loss
- muscular weakness
- malaise

Gastrointestinal

- anorexia
- nausea
- vomiting
- dysphagia
- constipation
- dyspepsia
- peptic ulceration
- pancreatitis

Cardiological

- short QT interval on ECG
- cardiac arrhythmias
- hypertension
- vascular calcification

Renal

- renal calculi
- nephrocalcinosis
- polyuria
- dehydration
- renal failure

Psychiatric

- drowsiness
- impaired concentration
- confusion
- psychosis
- depression
- personality changes
- coma

Ophthalmological

- corneal calcification

contractility of smooth muscle, which may explain the pathogenesis of dysphagia in patients with hypercalcaemia.

It is important to remember that the oesophagus consists of both skeletal muscle (upper third) and smooth muscle (lower two-thirds). Smooth muscle contains more calcium-dependent channels than skeletal muscle. Dysphagia, therefore, probably results from reduced smooth muscle contractions in the lower two-thirds of the oesophagus. Although the mechanism may not be fully understood, dysphagia should be regarded as a further symptom of hypercalcaemia.

Final diagnosis

Neuromuscular dysphagia due to hypercalcaemia resulting from metastatic carcinoma of the bronchus.

Keywords: hypercalcaemia; dysphagia

1 Grieve RJ, Dixon PF. Dysphagia: a further symptom of hypercalcaemia? *BMJ* 1983;286:1935-6.

A homesick student

G V McDonnell, T F G Esmonde

A 20-year-old, right-handed female student presented to a neurology clinic having developed depressive symptoms and become withdrawn. Her problems were initially attributed to homesickness. Over the next few months her condition gradually deteriorated. She developed drooling of saliva and retching and her speech became slurred. Her handwriting deteriorated and she was unsteady on her feet. There was urgency of micturition. These various symptoms had resulted in referral to ear, nose and throat and psychiatric services. A computed tomography (CT) scan of brain had been normal.

When first seen at the neurology clinic she was euphoric and mildly dysarthric with drooling. External appearances of the eyes were as shown in figure 1, funduscopy and eye movements being normal. There were dyskinetic movements of all four limbs with dystonic postures of the arms in flexion and adduction. There was normal power in all limbs with symmetrical reflexes. The left plantar response was extensor. She had mildly impaired concentration abilities but orientation and short-term recall appeared normal. There was a reduction in spontaneous speech output. Magnetic resonance imaging (MRI) of the brain was performed (figure 2). Full blood picture, renal function and liver function tests were all normal.

Figure 1 Corneal photograph of right eye

Questions

- 1 What does the corneal photograph show and what diagnosis does this suggest?
- 2 What biochemical tests would confirm the diagnosis?
- 3 What do the MRI scans show?
- 4 How would you treat this patient?
- 5 How should her family be managed?

Figure 2 MRI scans of brain, T2-weighted images (TR 4000 ms, TE 76 ms)

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Answers

QUESTION 1

The corneal photograph in figure 1 illustrates golden brown discolouration of the limbic region. This is a Kayser-Fleischer ring and is caused by copper deposition in Descemet's membrane. Given the history and clinical findings of a movement disorder, this suggests a diagnosis of Wilson's disease, although the rings themselves are not pathognomonic of the disorder, also being found in primary biliary cirrhosis, cryptogenic cirrhosis and chronic cholestasis.

QUESTION 2

Serum copper and caeruloplasmin should be measured, both of which would be expected to be low in value, whilst urinary copper excretion, which would be expected to be high, should be assessed by means of a 24-h collection. In this patient the following values were obtained: serum caeruloplasmin 0.03 g/l (normal range 0.21–0.58 g/l), serum copper 6.4 $\mu\text{mol/l}$ (12.6–26.7); urinary copper 5.0 $\mu\text{mol/24 h}$ (0.2–1.6).

QUESTION 3

The MRI scan of brain in figure 2 shows bilateral and symmetrical areas of abnormal increased signal intensity in the putamen and caudate nuclei (A), and midbrain (B).

QUESTION 4

Active management in cases of neurological Wilson's disease involves both dietary and pharmacological measures. Professional dietary advice and assessment is essential, the aim being to reduce dietary copper intake to < 1 mg/day. This involves avoidance of foods relatively rich in copper such as liver, mushrooms, cocoa, chocolate, nuts and shellfish.

D-Penicillamine has been a mainstay of treatment since its first use in 1956.¹ It is an effective copper-chelating agent which produces negative copper balance and subsequent detoxification of affected tissues. However, problems may arise with this compound in that sensitivity occurs in up to 20% of treated cases with the development of fever, leucopenia, rash and arthralgia. More seriously, it has been found that disastrous worsening can occur in as many as 50% of those with a neurological presentation treated with this drug, many of whom never recover.² A suggested mechanism for this is that the initial mobilisation and redistribution of hepatic copper causes higher levels of copper in critical areas of the brain. Another larger retrospective series has, however, shown that the initial deterioration with chelation therapy occurs less frequently (~21%) and may not be so crucial, with two-thirds of patients so affected eventually considered to have a good or very good outcome.³

Trientine dihydrochloride is another recently developed chelating drug. Although it has a similar mechanism of action to penicillamine and is therefore likely to share some of its toxicities, these may occur less frequently.

Because of these specific concerns regarding the use of chelating agents in neurological Wilson's disease, our patient was treated with a combination of zinc sulphate and a new agent, ammonium tetrathiomolybdate. Rather than causing a rapid mobilisation of copper, zinc acts by blockage of absorption of food copper and by blockage of reabsorption of endogenously secreted copper and puts the patient into a consistent negative copper balance in a way that does not suddenly cause an intense redistribution of copper.⁴ Ammonium tetrathiomolybdate forms a tripartite complex with copper and protein which renders the copper unavailable for uptake and removes it from toxic pools. There is evidence to suggest that this compound is more efficacious and better tolerated than penicillamine, with neurological deterioration being rare and recovery good to excellent in the majority of cases.⁵ As our patient regained independent mobility with resolution of her movement disorder and improvement in her speech, this report adds to the literature indicating the effectiveness of molybdate.

QUESTION 5

The early diagnosis of Wilson's disease is essential because many of the neurological features may not be fully reversible. As it has an autosomal recessive mode of inheritance, other siblings of the index case have a 25% chance of also being affected. Evidence of disease in as yet asymptomatic individuals should be sought by screening tests, including evaluation of urinary copper excretion and serum caeruloplasmin concentration.

Discussion

Wilson's disease is an autosomal recessive disorder characterised by a defect in copper metabolism; copper is unique among cations in that its balance is regulated by the liver. Although the exact nature of the defect is unclear, it causes a continual increase in tissue copper concentrations that become toxic to the liver, brain, kidney, eye and other organs. The responsible gene has been mapped to chromosome 13 and this has been cloned and found to encode for a cation-transporting P-type ATPase.⁶ Over 40 mutations in the gene have been found to be associated with the disease and there is some evidence to suggest that the extent of the genetic defect correlates with clinical severity, in that larger defects may result in the development of symptoms at an earlier age.

Hepatic presentation is the most common form in childhood, neurological presentation being most often observed, as in this case, in the late teenage years or adulthood. The mode of onset is very variable and often non-specific, making diagnosis initially difficult. Personality change is estimated to be the initial symptom in 32% of cases, other common symptoms at onset being speech disturbance, deterioration in school work, tremor, ataxia, drooling and dysphagia.⁷ The same large series of 136 patients found that the correct diagnosis was

Clinical features of advanced neurological Wilson's disease

- dysphagia and drooling
- rigidity
- bradykinesia
- flexed postures
- fixity of facial muscles with mouth agape
- virtual anarthria
- slow saccadic eye movements
- cerebellar ataxia

Box 1

made on first consultation with a doctor in less than one-third of cases. A diagnosis of psychiatric illness was made in almost 25% of cases, with a similar proportion given an organic diagnosis other than Wilson's disease. A classic misdiagnosis can arise from referral for a psychiatric opinion, where extrapyramidal features may be interpreted as being due to neuroleptic medication.

Apart from the common hepatic, neurological and psychiatric presentations, other organs may also be involved. Renal manifestations are many, with hypercalciuria and nephrocalcinosis being described. Proximal tubular dysfunction can result in Fanconi's syndrome with generalised aminoaciduria, glycosuria, hyperuricosuria and phosphaturia. Osteomalacia may result from phosphate wasting and chondrocalcinosis and osteoarthritis may arise from copper accumulation. Rapid uptake of copper into erythrocytes may produce an acute haemolytic anaemia. Myocardial involvement is reported and, in addition to Kayser-Fleischer rings, 'sunflower' cataracts may be seen in the eyes.

Previous MRI studies of the brain have indicated a predilection for copper deposition in certain areas, particularly the basal ganglia, cerebral white matter, midbrain, pons and cerebellum.⁸ Such a distribution has been demonstrated in this case and is borne out by the classic clinical syndrome manifest by patients with advanced disease (box 1). The onset can, however, be insidious and non-specific as illustrated here, with behavioural problems and intellectual decline preceding the onset of hard neurological signs and movement disorders.

One of the characteristic stigmata of Wilson's disease are Kayser-Fleischer rings, deposits of copper producing golden-brown discolouration in the peripheral cornea. Their earliest appearance consists of coloured crescents at the superior and inferior quadrants of the cornea that eventually become circumferential. Until recently they had been considered pathognomonic for Wilson's disease but several associations are now known (box 2). They had also been considered an invariable component in patients with neurological involvement but exceptions have recently been documented.⁹ As in this case, the rings may be readily

Diseases associated with Kayser-Fleischer rings

- Wilson's disease
- primary biliary cirrhosis
- chronic cholestasis
- cryptogenic cirrhosis

Box 2

Wilson's disease: learning points

- neurological presentation is more common in late adolescence and adulthood
- behavioural problems and cognitive decline may precede other neurological signs
- normal liver function tests do not preclude the diagnosis
- serum caeruloplasmin is normal in 5% of cases
- Kayser-Fleischer rings can only be excluded by slit-lamp examination
- penicillamine may cause irreversible deterioration in neurological manifestations
- ammonium tetrathiomolybdate should be considered as a first-line therapy
- potentially presymptomatic siblings must be identified by screening test

Box 3

detected by the naked eye. However, in other circumstances they may be easily missed unless sought by an experienced ophthalmologist using a slit-lamp.

In conclusion, this case illustrates the importance of contemplating the diagnosis of Wilson's disease in young patients presenting with behavioural disorders, extrapyramidal, or cerebellar signs since, although uncommon, it is so eminently treatable if recognised early and managed appropriately. Kayser-Fleischer rings are a characteristic feature but are neither pathognomonic for, nor an essential element in, those with neurological manifestations of the disease. Normal liver function tests do not preclude the diagnosis. Although the most appropriate initial treatment is not clearly established, caution should be exercised in the use of penicillamine and alternative therapy with zinc sulphate and/or ammonium tetrathiomolybdate should be considered. Finally, since prophylactic therapy in affected but presymptomatic patients can prevent the onset of symptomatic disease, the prompt diagnosis of affected presymptomatic siblings by means of screening tests should be a priority.

Final diagnosis

Wilson's disease.

Keywords: Wilson's disease; Kayser-Fleischer rings; copper; penicillamine; ammonium tetrathiomolybdate

The authors wish to acknowledge the assistance of Dr Steven McKinstry, Consultant Neuroradiologist, Royal Victoria Hospital in the interpretation and preparation of the MRI scans.

- 1 Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med* 1956;21:487-95.
- 2 Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurological syndrome in patients with Wilson's disease with initial penicillamine therapy. *Arch Neurol* 1987;44:490-4.
- 3 Walshe JM, Yealland M. Chelation treatment of neurological Wilson's disease. *Q J Med* 1993;86:197-204.
- 4 Brewer GJ, Turkay A, Yuzbasiyan-Gurkan V. Development of neurologic symptoms in a patient with asymptomatic Wilson's disease treated with penicillamine. *Arch Neurol* 1994;51:304-5.
- 5 Brewer GJ, Johnson V, Dick RD, Kluin KJ, Fink JK, Brunberg JA. Treatment of Wilson disease with ammonium tetrathiomolybdate. II. Initial therapy in 33 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 1996;53:1017-25.
- 6 Tanzi RE, Petrukhin K, Chernov I, *et al*. The Wilson's disease gene is a copper transporting ATPase with homology to the Menkes disease gene. *Nat Genet* 1993;5:344-50.
- 7 Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. *J Neurol Neurosurg Psychiatry* 1992;55:692-6.
- 8 King AD, Walshe JM, Kendall BE, *et al*. Cranial MR imaging in Wilson's disease. *AJR* 1996;167:1579-84.
- 9 Demirkiran M, Jankovic J, Lewis RA, Cox DW. Neurologic presentation of Wilson disease without Kayser-Fleischer rings. *Neurology* 1996;46:1040-3.

Images in medicine

Pneumatosis cystoides intestinalis

A 64-year-old woman was admitted to our hospital for a closer examination of occult blood in the stool. She appeared to be healthy, but physical examination revealed a soft elastic mass in her right lower abdomen. Laboratory examinations showed no abnormality of blood chemistry and that red and white blood cell counts were within the normal ranges. Abdominal X-ray revealed numerous round radiolucencies in the right side of the colon (figure

1), which were shown as honeycomb-like lesions by computed tomography. Total colonoscopy showed multiple submucosal cysts containing gas in the ascending and transverse colons (figure 2). She was therefore diagnosed as having pneumatosis cystoides intestinalis.

We should bear in mind that pneumatosis cystoides intestinalis can be easily diagnosed by the characteristic numerous round radiolucencies on abdominal X-ray, which can eliminate unnecessary invasive and expensive further examinations.

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Accepted 4 January 1999

Figure 1 Abdominal X-ray

Figure 2 Colonoscopic findings of the transverse colon