Self-assessment questions

Unusual findings in a patient taking warfarin

R J Morgan, J B Bristol

A 60-year-old man was admitted with a 48-hour history of left-sided abdominal pain. He was receiving anticoagulation therapy with warfarin for a prosthetic aortic valve. His INR on admission was 4.1. Initial full blood count, urine microscopy and plain abdominal radiographs were normal. He underwent an abdominal computed tomography (CT) scan (figure 1).

Within 24 hours the patient developed ecchymoses in the peri-umbilical region, both flanks, and down the left lower limb from the thigh to the lateral aspect of the foot (figure 2).

Figure 1 Abdominal CT scan

Figure 2 Cutaneous haemorrhagic discoloration of (A) the peri-umbilical region, and (B) the flank and lower limb, involving the foot

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Questions

- 1 What is the abnormality (arrowed) shown on the abdominal CT scan (figure 1)?
- 2 Who first described these appearances?

Answers

QUESTION 1

The CT scan shows a left-sided retroperitoneal haematoma.

QUESTION 2

Cullen's sign¹ was originally described as peri-umbilical ecchymoses in ruptured extra-uterine pregnancy, but has come to be considered a sign of acute haemorrhagic pancreatitis. Grey-Turner described haemorrhagic discoloration of the flanks in acute pancreatitis² and Fox described discoloration of the thigh due to extraperitoneal haemorrhage.³

Discussion

These appearances can be caused by a number of other conditions besides acute pancreatitis; for example, Cullen's sign can occur as a result

of splenic rupture.⁴ Retroperitoneal haematoma is an unusual cause of cutaneous haemorrhagic discoloration. Spontaneous retroperitoneal haematoma has been described in anticoagulated patients,⁵ although it is a rare occurrence when the INR is within the therapeutic range. Discoloration of the foot caused by retroperitoneal haematoma (or any other form of intra-abdominal haemorrhage) has not been previously reported.

Our patient was managed conservatively and re-established on warfarin at a lower dose. He was discharged home after 7 days with an INR of 2.8.

Final diagnosis

Retroperitoneal haematoma.

Keywords: retroperitoneal haematoma; Cullen's sign; warfarin

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New weakness in a critically ill patient

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A 24-year-old woman was admitted to her local hospital with an infective exacerbation of asthma. Apart from asthma, which had resulted in several previous uncomplicated admissions to hospital, she was otherwise well. She had no history of any neuromuscular problems and neurological examination on admission was unremarkable. She was treated with intravenous hydrocortisone (200 mg 6 hourly), aminophylline and augmentin and nebulized salbutamol and ipratropium bromide, but became increasingly wheezy and distressed and required mechanical ventilation. Arterial blood gas analysis on 60% oxygen prior to ventilation revealed the pH to be 7.09, and the partial pressures of O₂ and CO₂ to be 19 and 10.5 kPa, respectively. Other investigations were unremarkable, apart from a peripheral leucocytosis of $14 \times 10^9/l$. In the intensive care unit, muscle relaxation was achieved with intravenous suxamethonium, atracurium and a continuous infusion of vecuronium, and sedation with intravenous midazolam, propofol and alfentanil. Initial treatments were continued, but the dose of hydrocortisone was increased to 200 mg every 2 hours and intravenous cefotaxime and metronidazole were introduced.

On day 3 the patient was transferred to the regional intensive care unit because of deteriorating renal function. This resolved spontaneously without the need for dialysis, the maximum serum urea and creatinine levels being 24 mmol/l and 137 μ mol/l, respectively. On one occasion when renal function was recovering serum potassium was 2.4 mmol/l; all other electrolytes including serum phosphate, calcium and magnesium were unremarkable.

On day 11 airway obstruction was not evident on examination. On day 12 muscle relaxants, which had been administered from admission to the intensive care unit, and sedation were stopped. Mechanical ventilation was required for a further 8 days, however, because of severe generalised weakness. Examination on day 14 revealed the patient to be alert and obeying commands. A partial left sixth nerve palsy, mild facial weakness and flaccid tone in the limbs were noted. Power in the limbs was graded as a flicker of movement proximally and grade 2–3 distally. All deep tendon reflexes were absent. Sensory examination was normal. The patient was transferred to the neurology department on day 22 being able to maintain adequate ventilation although she was still profoundly weak.

Questions

- 1 What are the most probable causes of this patient's new weakness resulting in difficulty weaning from the ventilator?
- 2 What investigations should be performed to confirm the diagnosis?
- 3 What is the prognosis for recovery?

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Answers

QUESTION 1

The decreased tone, areflexia and preserved mental state in this patient with severe weakness suggest a neuromuscular disorder. A central disorder, of either the brain or spinal cord, causing acute severe weakness can be difficult to exclude in patients in the intensive care setting because of difficulties with communication. A central disorder was felt to be unlikely in our patient, however, as upper motor neuron signs were never detected at any stage. Likewise a spinal cord lesion as the sole cause of the patient's weakness was excluded because she had cranial nerve signs. Where the possibility of a spinal lesion exists, however, the spinal cord should be imaged by magnetic resonance scanning. The principal neuromuscular diseases causing new generalised weakness in critically ill patients are shown in box 1.

Of the neuropathies, critical illness polyneuropathy may be the most common cause of weakness in critically ill patients. This condition is thought to result from inadequate perfusion of the peripheral nerves.¹ It is usually associated with encephalopathy and multi-organ failure and often results in more severe distal than proximal weakness,¹ all of which were in contrast to the findings in our patient.

Guillain-Barre syndrome (of which acute inflammatory demyelinating polyradiculoneuropathy and acute motor axonal neuropathy are two variants) results in flaccid weakness with or without prominent sensory symptoms and typically occurs two weeks or so after an infective illness, as was the case for our patient. Prompt recognition of this condition is important because early treatment with plasma exchange or immunoglobulin improves outcome.

Acute intermittent porphyria often results in abdominal pain, psychiatric disturbances or autonomic dysfunction, none of which occurred in this case.

Causes of new weakness in critically ill patients

Neuropathies

- acute inflammatory demyelinating polyradiculoneuropathy
- acute motor axonal neuropathy
- critical illness polyneuropathy
- acute intermittent porphyria

Neuromuscular-transmission disorders

- prolonged neuromuscular blockade from muscle relaxants
- myasthenia gravis
- organophosphate poisoning

Myopathies

- acute necrotizing myopathy
- critical illness myopathy

Biochemical abnormalities

- hypokalaemia
- hypophosphataemia
- hypocalcaemia
- hypermagnesaemia

Box 1

Although myasthenia gravis often presents with weakness, the extreme nature of the weakness in our patient was not typical of this condition. In addition, the minimal involvement of the extra-ocular muscles and absent reflexes (which are typically normal in myasthenia gravis) made this diagnosis unlikely.

Prolonged blockade at the neuromuscular junction from the long-term administration of muscle relaxants, typically results in flaccid paralysis, which may be very severe, and areflexia.² It usually occurs in the context of impaired hepatic or renal function and has mostly been described in cases where vecuronium has been administered; two of these precipitants were present in our case. No cholinergic features (miosis, sweating, bradycardia) were present, making inadvertent organophosphate exposure unlikely.

Clinically, it is impossible to exclude either acute necrotizing myopathy or critical illness myopathy as the cause of this patient's weakness. Both may result in flaccid weakness with areflexia and little or no sensory disturbance in critically ill patients exposed to neuromuscular blocking agents or high-dose corticosteroids.

QUESTION 2

The minimum investigations necessary to differentiate between the various causes of weakness in the critically ill patient, once simple biochemical abnormalities have been excluded, are shown in box 2.

The creatinine kinase level was never elevated in our patient, essentially excluding acute necrotizing myopathy. Likewise cerebrospinal fluid (CSF) analysis performed 11 days after the onset of weakness was normal. Although this made Guillain-Barre syndrome, or its related conditions unlikely (the CSF protein usually being elevated in these conditions) it did not completely exclude them. Nerve conduction studies performed 16 days after the onset of the weakness, however, did not reveal

Investigations required to determine cause of weakness in critically ill patient.

Serum

- potassium, phosphate, calcium, magnesium, urea
- immunoglobulins and plasma protein electrophoresis
- creatinine kinase

Urine

- porphyrins

Cerebrospinal fluid

- protein
- cell count

Electrophysiology

- nerve conduction studies
- repetitive nerve stimulation
- electromyography

Muscle biopsy

Box 2

the typical findings of Guillain-Barre syndrome or its variants, such as slowing of peripheral nerve conduction or conduction block. Critical illness polyneuropathy or a disease of the neuromuscular junction were not excluded by these investigations. Electromyographic sampling of muscle, however, did not reveal the features of denervation, which would be expected for all of the potential neuropathic causes of weakness, including critical illness polyneuropathy. Repetitive nerve stimulation likewise did not show the decremental response typical of prolonged neuromuscular blockade or myasthenia gravis. Instead, electromyography demonstrated small, brief polyphasic motor unit potentials, with good recruitment and a complete interference pattern, in keeping with a myopathic process. Muscle biopsy of the left quadriceps confirmed a myopathic process demonstrating features such as diffuse myofibre degeneration. Electron microscopy of the same specimen also showed loss of thick filaments as has been described in critical illness myopathy.³ By a process of exclusion, critical illness myopathy was therefore felt to be the cause of this woman's weakness.

QUESTION 3

Recovery in any critically ill patient who develops new muscle weakness is ultimately dependent on the prognosis of the primary illness which necessitated admission to the intensive care unit. If the patient survives this illness, however, it is the cause of the weakness that will

determine how much return of power that will occur. Critical illness myopathy is increasingly being recognised as a cause of new weakness in critically ill patients. This condition, first described in 1977 by MacFarlane and Rosenthal,⁴ typically results in difficulty weaning from the ventilator and is associated with diffuse weakness of a varying degree, without or without ophthalmoplegia or facial weakness, attenuation of reflexes, subtle or no sensory disturbance, and preservation of higher functions.⁵ Usually, in addition to being critically ill, patients who develop this condition have had a febrile illness, or have been septicemic, and have received high doses of corticosteroids and/or neuromuscular blocking agents. In contrast to other causes of weakness in this setting, such as critical illness polyneuropathy which often occurs in the absence of neuromuscular blocking agents or steroid administration, the outlook for recovery has generally been reported as being good.⁵ As recovery is spontaneous the need for specific therapies, such as plasmapheresis or human immunoglobulin for Guillain-Barre syndrome which are more often associated with complications in these patients, is also unnecessary.

Final diagnosis

Critical illness myopathy.

Keywords: critical illness myopathy; muscle weakness

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A woman with amenorrhoea

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A 26-year-old woman was referred by her general practitioner with primary amenorrhoea. She denied galactorrhoea or headaches. She had undergone ligation of a patent ductus arteriosus at 2 years of age and was noted in childhood to have a partial hearing defect in her right ear. On examination she was a phenotypically normal female with a BMI of 23.2 kg/m². She had Tanner stage II breast and pubic hair development. Investigations revealed a normal full blood count, urea and electrolytes, with a glucose of 5 mmol/l, prolactin of 100 mU/l (normal < 400 mU/l). Hypogonadotrophic hypogonadism was confirmed with a low plasma oestradiol of 108 pmol/l (normal > 130), luteinising hormone (LH) < 0.5 U/l and follicle-stimulating hormone (FSH) < 0.5 U/l. She had impaired responses to LHRH stimulation of LH < 0.5 U/l and FSH 0.6 U/l. Dynamic testing of pituitary function revealed a normal growth hormone, cortisol and prolactin response to insulin-induced hypoglycaemia. Thyroid function tests, pituitary magnetic resonance imaging, and karyotype were normal.

Questions

- 1 What other clinical test would be useful?
- 2 What is the diagnosis?

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Answers

QUESTION 1

Test her sense of smell. This patient had an absent sense of smell to standard testing with coffee, lemon juice and varying concentrations of propionic acid.

QUESTION 2

Kallmann's syndrome.

Discussion

In this case, the association of hypogonadotrophic hypogonadism, deafness and anosmia confirms the diagnosis of Kallmann's syndrome. Kallmann's syndrome is the commonest cause of isolated gonadotropin deficiency¹ with a predominantly male predisposition. It can occur in a familial setting, though the majority of cases are sporadic.

Although the exact cause of Kallmann's syndrome remains to be identified, it is believed that there is a failure of migration of the LHRH neurones to the median eminence of the hypothalamus.² According to Rimoin and Shimke,³ Kallmann's syndrome represents a complex spectrum of developmental anomalies which include midline cleavages of the embryonic forebrain, aplasia of the olfactory bulb and tract with midline dysplasia of the face causing abnormalities like cleft lip, cleft palate, congenital deafness and colour blindness. Other developmental abnormalities reported in association with Kallmann's syndrome include gut malrotation, renal agenesis and congenital heart defects.¹

In 1960 Gauthier⁴ for the first time reported a case of a young woman with olfactogenital dysplasia (Kallmann's syndrome) who had died of an Ebstein anomaly. Since then there have been seven other case reports of Kallmann's syndrome in association with other cardiac abnormalities, these include right aortic arch, 2:1 atrioventricular block and Wenckebach phenomenon, atrial septal defect, and a complex case of transposition of the great vessels which required heart transplantation.¹

Kallmann's syndrome is genetically heterogeneous and may be inherited in an autosomal dominant or recessive pattern. In some forms

Clinical features of Kallmann's syndrome

- anosmia
- deafness
- hypogonadotrophic hypogonadism
- cleft lip and cleft palate
- rarely, congenital heart defects, renal agenesis

of inheritance there is a defect in the KALIG-1 gene.² It is speculated that this gene may have a direct effect on axonal outgrowth and is required for the normal migration of the embryonic cells that develop within the olfactory bulb and the hypothalamic nuclei that subsequently secrete gonadotropin-releasing hormone.² The KALIG-1 gene may also be involved in the recognition mechanisms which occur between LHRH nuclei and olfactory nuclei, as well as in the modulation of migrating cardiac cells during embryonic development, which may account for the association of certain types of congenital heart defects with Kallmann's syndrome.² This is supported by the demonstration of aorticopulmonary septal defects following the removal of areas within the occipital neural crest, the area from which the presumptive cardiac cells originate in chick embryos.⁵

To our knowledge there have been no reports of Kallmann's syndrome in association with patent ductus arteriosus. The significance of this and other cardiac defects in association with Kallmann's syndrome is unclear as it may represent a purely chance occurrence. However, it may also reflect a true association between Kallmann's syndrome and congenital heart defects, due to the putative mechanism outlined previously.

Final diagnosis

Kallmann's syndrome.

Keywords: patent ductus arteriosus; Kallmann's syndrome; heart defects

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Acute epigastric pain and recurrent vomiting in an elderly man

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A 76-year-old previously asymptomatic man presented to the emergency room with a 4-hour history of severe epigastric pain. This was accompanied by vomiting of food contents followed by repeated dry heaves. Examination was remarkable for tenderness in the epigastrium with no abdominal rigidity and normal bowel sounds. A nasogastric tube could not be inserted despite repeated attempts. The medical history was significant for a motor vehicle accident 2 years prior to admission that resulted in fracture of the left humerus, three left-sided rib fractures, and a splenic laceration that did not require surgery. An upright X-ray of the abdomen (figure 1) followed by computed tomography (CT) scan (figure 2) of the abdomen were performed.

Figure 1 Upright X-ray of the abdomen

Figure 2 Abdominal CT scan

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Questions

- 1 What is the unusual finding in figure 1?
- 2 What are the CT scan findings in figure 2?
- 3 What test would confirm the diagnosis?

Answers

QUESTION 1

There is a single air fluid level in the midline but the gastric bubble normally seen in the left hypochondrium is absent.

QUESTION 2

The CT scan shows an abnormal axis of the stomach with the antrum (open arrow) anterior and lateral to the gastro-oesophageal junction (closed arrow) and at the same level as the gastric fundus. These findings are suggestive of a gastric volvulus.

QUESTION 3

A barium study would confirm the diagnosis. This study showed the greater curvature of the stomach (open arrow) located superior to the lesser curvature with the cardia and pylorus at the same transverse level confirming the presence of an organo-axial gastric volvulus (figure 3).

Figure 3 Barium study

Discussion

A gastric volvulus can be classified based on the axis of rotation (organo-axial, mesentero-axial or combined), severity (acute or chronic), extent (total or partial), direction (anterior or posterior) or aetiology (secondary or idiopathic).¹

The characteristic triad of an acute gastric volvulus (box) was described in 1904 and validated in subsequent studies.² Chronic gastric volvulus usually manifests with vague abdomi-

Characteristic triad of an acute gastric volvulus

- sudden onset of constant and severe upper abdominal pain
- recurrent retching with production of little vomitus
- inability to pass a nasogastric tube

nal symptoms such as dyspepsia, heart burn, eructation, nausea and vomiting long before the diagnosis is made.³

Our patient had an acute organo-axial gastric volvulus which was diagnosed by an abdominal CT scan and confirmed by a barium study. An unusual discovery was the absence of an associated hiatal hernia which is usually present in patients with an organo-axial gastric volvulus. An extensive search of the literature located only two reports of a CT-scan mediated diagnosis of gastric volvulus and both reports were of patients with a hiatal hernia or an intra-thoracic stomach.^{4 5}

The finding of a single midline air fluid level in the upright abdominal radiograph was initially thought to be due to an associated hiatal hernia. However, although a very high dome of the diaphragm was noted during surgery in our patient, no defects or hernias were detected. Acute gastric volvulus is a rare condition but one which needs to be diagnosed quickly to avoid life-threatening complications like ischaemic necrosis, haemorrhage and gangrene. While a CT scan is not necessary to diagnose gastric volvulus, we suggest that a CT scan finding of the stomach in an unusually high position or an abnormal axis of the stomach with the antrum and gastro-oesophageal junction at the same transverse level in a patient with acute abdominal pain and vomiting should elicit the suspicion of a gastric volvulus.

Final diagnosis

Acute organo-axial stomach volvulus.

Keywords: stomach; volvulus; computed tomography

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An elderly man with dysphasia and pyrexia

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An 85-year-old man presented with a 3-week history of headache, reduced mobility and dysphasia. The headache was unilateral affecting the left side. His reduced mobility was associated with varying levels of weakness of the right arm and leg. His dysphasia was reflected in problems reading the newspaper, and speaking to his wife, as well as understanding what his wife was saying to him. On examination he was found to be alert and orientated in time, place and person, scoring an abbreviated mental test score of 9/10. Neurological examination revealed a right upper motor lesion of cranial nerve VII, increased reflexes in the right arm and leg, and a dysphasia which was both expressive and receptive. In addition he had a temperature of 37.5°C. He had a normal full blood count, routine biochemistry and chest X-ray. Blood cultures were negative. His C-reactive protein was 11 mg/l. Urgent computed tomography (CT) of the brain was organised (figure 1). Following treatment the patient's condition improved gradually over a month. At discharge he had minimal dysphasia and walked independently with ease. Two months later he developed a peripheral sensory neuropathy of a glove and stocking distribution. Serum vitamin B12, folate and thyroid function tests were normal. There was no history of alcoholism, diabetes mellitus or a connective tissue disorder. Following a further adjustment to his treatment he eventually fully recovered (figure 2).

Figure 1 Cranial CT scan with contrast at presentation

Figure 2 Cranial CT scan with contrast after 8 months

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Questions

- 1 Might the medical history help?
- 2 What is the probable initial diagnosis?
- 3 How would you manage his problem?
- 4 Why did he develop peripheral neuropathy?

Answers

QUESTION 1

Yes. His medical history revealed that about 40 years earlier he had been diagnosed as having a left-sided cerebral abscess secondary to mastoiditis. Both were treated surgically. There are three main categories of predisposing factors for cerebral abscesses. Firstly, a contiguous source of infection such as dental abscess or otitis media accounts for approximately 47% of cases. Secondly, haematogenous spread from a distant focus such as bronchiectasis or bacterial endocarditis can account for 25% of causes. Cranial trauma accounts for approximately 8–13%. In 15–20% of cerebral abscess no cause can be found.¹

QUESTION 2

Cranial CT scan showed ring-enhancing lesions in the left temporo-parietal area suggestive of cerebral abscesses or possibly metastatic malignant deposits (figure 1). The clinical picture supported the former diagnosis.

QUESTION 3

In consultation with local neurosurgeons a decision was made to opt for initial medical treatment and assess response with serial cranial CT scans. Treatment initially involved a 2-week regime of intravenous cefotaxime, metronidazole and ciprofloxacin. This was followed by long-term oral ciprofloxacin and metronidazole. There was resolution of the cerebral abscesses on CT scan 8 months after initiating antibiotics (figure 2). As no organism was isolated from the abscesses, treatment was empirical. The organisms isolated in cerebral abscesses include streptococci (*Streptococcus intermedius* group, including *S. angiosus*) in 60–70% of cases, enterobacteriaceae in 23–30% of cases, bacteroides and parvotella in 20–40% of cases and *Staphylococcus aureus* in 10–15% of cases.² Evidence for the use of met-

Learning points

- beware of patients with stroke and a history of ear disease
- cerebral abscesses can recur late and be managed successfully medically
- long-term metronidazole can cause peripheral neuropathy

ronidazole was provided by Ingham *et al*, who showed it to cross the blood–brain barrier and penetrate cerebral abscesses well.³ In Sjolín's series, a combination of cefotaxime and metronidazole was shown to be effective in treatment of cerebral abscesses.⁴ Success of ciprofloxacin in the treatment of cerebral abscesses has been reported.⁵

QUESTION 4

Metronidazole was stopped as it was suspected to be the cause of the peripheral neuropathy, and the patient was continued on ciprofloxacin 250 mg bid. His peripheral neuropathy had mainly resolved 6 months after discontinuation of metronidazole. This has been a well documented side-effect since 1976 when Coxon and Pallis first suggested metronidazole to be a cause of neuropathy.⁶ The degree of neuropathy is dose- and duration-dependent. Signs of neuropathy are reversed within 4–48 months of cessation of metronidazole treatment.⁷

Final diagnosis

Cerebral abscesses, followed by peripheral neuropathy as a side-effect of metronidazole treatment.

Keywords: adverse drug reaction; metronidazole; peripheral neuropathy

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Sudden hearing loss following acute hepatitis

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A 35-year-old previously healthy physician was admitted to the emergency room with a fever up to 40°C, extreme weakness and dark urine. The physical examination was remarkable for right upper quadrant abdominal tenderness and mild splenomegaly. He denied sore throat or direct contact with blood products. Laboratory studies disclosed elevated liver enzymes, hyperbilirubinemia and bilirubinuria. A diagnosis of acute hepatitis was established. Initially, all serologic viral studies were negative. However, a late seroconversion for IgM to the early antigen (EA) of Epstein-Barr virus (EBV) in the presence of negative antibodies to Epstein-Barr nuclear antigen (EBNA), followed by a rise in the IgG titres to EA and EBNA were observed, indicating EBV to be the causative agent of the hepatitis. During follow-up examinations in our out-patient clinic, a gradual convalescence and normalisation of the abnormal liver function tests were observed.

Four weeks later the patient complained of a sudden hearing loss in his right ear which he had noticed subsequent to an examination of his patients with a stethoscope and after using a telephone handset with his right ear. He did not complain of tinnitus, nausea, vomiting or vertigo. The physical examination was normal, with a negative Romberg test and without nystagmus. A comprehensive audiologic assessment revealed a bilateral normal ear-drum with a normal pure-tone air and bone conduction (Weber and Rinne tests). The pure tone threshold analysis results are presented in figure 1. Treatment was initiated and the audiogram was repeated 10 days later (figure 2).

Figure 1 Audiogram performed on admission

Figure 2 Audiogram performed 10 days after initiation of therapy

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Questions

- 1 What abnormality is demonstrated on the admission audiogram (figure 1) ?
- 2 What is the diagnosis and its cause ?
- 3 What are the possible additional common aetiologies of the presented disorder ?
- 4 Describe the changes in the audiogram presented in figure 2 compared to that in figure 1.

Answers

QUESTION 1

The audiogram performed on admission demonstrates a decrease of 20–35 dB hearing level at low to intermediate frequencies (250–1000 Hz) in the right ear. The left ear is normal.

QUESTION 2

The patient has a classic sudden sensorineural hearing loss following a preceding EBV infection. The performance-intensity function, including a speech reception threshold (SRT) analysis and a speech discrimination assay, resulted in a normal finding for the left ear, however, it was pathological for the right ear (SRT, right ear = 25 dB). A negative reflex decay with normal acoustic reflexes were observed. Computed tomography of the posterior fossa, an electronystagmogram, and auditory brainstem response testing were normal.

QUESTION 3

In the presented case, a preceding EBV infection yielded hearing loss by either gaining access to the inner ear, leading to several pathophysiologic changes, or causing an immune-mediated reaction, both resulting in the same impairment leading to sudden deafness. Additional common causes of sudden hearing loss include acoustic neuromas, Ménière's disease, ototoxic drugs and multiple sclerosis.

QUESTION 4

Following initiation of carbogen inhalations, prednisone and oxipurine treatment, the patient experienced a rapid improvement in auditory acuity. The repeated audiogram demonstrates complete recovery of the right ear hearing. No hearing disturbances were noticed during a 12-month follow-up.

Discussion

Sudden hearing loss (SHL) is a term generally used to refer to hearing loss of sensorineural origin evolving over a period of a few hours to a few days. Acoustic neuromas, Ménière's disease, multiple sclerosis and ototoxic drugs are among the most common causes. In some cases, the aetiology remains unknown. Idiopathic SHL has been reported to have an incidence of between 5 to 20 new cases per 100 000 population per year.¹ Several suggested theories attempt to elucidate the aetiopathogenesis of idiopathic SHL, including autoimmune diseases, a vascular insult and viral infections.

Several viruses have been strongly implicated as having a causative role in the pathogenesis of SHL. Veltri *et al*² and Wilson *et al*³ studied the incidence of seroconversion to several viruses in a group of patients presenting with SHL compared with a healthy control group. In the SHL group of patients, there was a significantly higher incidence of seroconversion to mumps, rubella, rubeola, measles, herpes simplex, varicella-zoster, cytomegalovirus and influenza viruses types A & B. Moreover, in some

patients with SHL, viruses were directly identified in the inner ear by either immunofluorescent methods⁴ or perilymph cultures.⁵

EBV has only rarely been associated with SHL. The table summarises 14 reported cases of EBV infection complicated by hearing loss.^{6–14} It usually occurs in young adults with infectious mononucleosis, their ages ranging between 7 and 58 years (mean, 21 years), with a considerable female predominance (M:F, 5:9). The hearing loss usually appears in the convalescent phase of the disease, but may infrequently be a presenting symptom.¹² The mean time between the acute illness to the appearance of hearing loss is 6 weeks, ranging from 2.5 weeks to 3.5 months (table). Both ears are equally vulnerable. The overall percentage of patients with bilateral SHL is 4–17%.³ However, six out of the 14 (43%) cases of SHL attributed to EBV infection involved both sides (table). Audiometry analysis displays mild to severe impairment of intermediate or high frequencies. In rare cases, the spectrum of low frequencies is also involved.

EBV is an ubiquitous pathogen infecting most (>90%) of the world's population. It is associated with both benign disorders, such as infectious mononucleosis, and malignant disorders, such as Burkitt lymphoma and nasopharyngeal carcinoma. Less frequent manifestations include pneumonitis, cerebritis, mono- or polyneuritis, Guillain-Barre syndrome, myocarditis, pericarditis, thrombocytopenia, and agranulocytosis.¹⁵

Various neurologic manifestations have been associated with infectious mononucleosis, including Guillain-Barre syndrome, Bell's palsy, meningoencephalitis, and transverse myelitis.¹⁶ These complications may occur in the absence of a clinically apparent infectious mononucleosis.

The exact mechanism leading to SHL following EBV infection has not been clearly determined. Schunknecht *et al*¹⁷ studied the histopathology of temporal bones from SHL patients, and demonstrated atrophy of the organ of Corti, tectorial membrane, stria vascularis, cochlear nerve and vestibular organ. Identical pathologic findings were discovered in patients with established viral labyrinthitis. These authors suggested that viral particles gain access to the membranous cochlea by haematogenous spread (viraemia), replicate locally and lead to rapid pathophysiologic changes resulting in reduced blood flow to the inner ear that is frequently reversible but may be extremely destructive and result in permanent hearing loss.

Nevertheless, the scarcity with which EBV is associated with hearing loss, in addition to the significant attention that immune-mediated SHL has received, led Williams *et al*¹³ to propose that, in certain susceptible individuals, a temporary cellular immunosuppression, which accompanies normal recovery from EBV infection, may provide an opportunity for reactivation of a viral agent already present in the inner ear. Thus, it appears that the role of EBV in sudden deafness has yet to be clarified.

The therapy currently advocated for SHL includes carbogen inhalations (a mixture of

Table Sudden hearing loss associated with EBV – clinical data

Ref	Age (years), sex	Clinical manifestations of infectious mononucleosis	Lag period*	Impaired frequencies**	Side	Tinnitus	Additional neurologic signs	Outcome
6	58, M	sore throat, cervical lymphadenopathy	8 weeks	N/R	right	–	Ataxia, diplopia, Guillain-Barre syndrome	Complete recovery
7	18, F	sore throat, malaise, high fever, cervical lymphadenopathy	2.5 weeks	60 dB loss at 2000 Hz	N/R	–	Mental confusion, memory loss, ataxia, bilateral papilloedema	Complete recovery
8	17, M	fatigue, anorexia, sore throat, high fever, cervical lymphadenopathy, hepatomegaly	2 weeks	100 dB loss at 4000 Hz	right	+	Vestibular nerve involvement	Slight recovery
9	20, F	high fever, lymphadenopathy	8 weeks	40 dB loss at 2000 Hz	left	–	Cranial neuropathy of V and VII, vertical nystagmus	Slight recovery
10	23, F	anorexia, autoimmune haemolytic anemia, acute hepatitis	6 weeks	60 dB loss at 6000 Hz	left	+	Tinnitus	Slight recovery
11	25, F	fatigue, anorexia, sore throat, lymphadenopathy	N/R	25 dB loss at 8000 Hz	bilateral	–	None	Persistent
	32, F	anorexia, fatigue, lightheadedness, sore throat, cervical lymphadenopathy	N/R	35-dB loss at 8000 Hz	bilateral	–	None	Persistent
12	16, M	none	N/R	40 dB loss at 4000 Hz	bilateral	–	Ataxia, dysmetria, dysidiadochokinesia, dysarthria, bilateral nystagmus	Persistent
13	14, F	N/R	3.5 months	80 dB loss at 6000 Hz	bilateral	+	None	Persistent
	7, F	N/R	months	45-dB loss at 3000 Hz	bilateral	+	None	Persistent
	9, M	N/R	4 weeks	60-dB loss at 6000 Hz	left	+	None	Persistent
			5 months	80-dB loss at 500 Hz	right	+		
14	12, F	excessive tiredness	3 weeks	60 dB loss at 8000 Hz	bilateral	–	Seizures, acute psychotic reaction, acute encephalopathy	Persistent
	14, F	excessive tiredness, headache, exudative tonsillitis	4.5 weeks	80-dB loss at 2000 Hz	right	–	Dizziness	Persistent
Present case	35, M	high fever, malaise, acute hepatitis	4 weeks	35 dB loss at 500 Hz	right	–	None	Complete recovery

*The lag period is calculated from the time of infectious mononucleosis diagnosis to the notice of hearing loss.

**The specific frequency indicated in the table is the one most damaged within the range of frequencies found impaired at audiometry analysis.

N/R - Not reported.

95% oxygen and 5% carbon dioxide) in order to improve pO_2 levels in the perilymph¹⁸ and systemic steroid therapy. The latter treatment is based on its anti-inflammatory effect in viral infections. It is noteworthy that no controlled studies have been performed with any of the suggested forms of therapy, which makes it difficult to judge whether a suggested therapy would result in a higher recovery rate than a spontaneous recovery.

Our review indicates a poor prognosis for the recovery of hearing in SHL following EBV infection. Of 14 reported cases, only three had complete recovery, three had slight recovery, and eight (57%) remained with permanent deafness (table). Generally, sudden deafness has a better prognosis than cases associated with EBV infection; one-third of patients have a return of normal hearing, one-third are left with a 40–80 dB speech reception threshold, and one-third have a total loss of useful hearing.¹⁹ Spontaneous recovery of normal hearing is more likely to occur if the deafness is not associated with vertigo or advanced age. Once recovery of hearing begins, it is likely to

take place very rapidly in a matter of a few days. The longer the delay between the onset of deafness and the onset of recovery, the worse the prognosis for complete recovery.²⁰ There is no difference in the outcome of patients in whom the hearing loss is isolated compared with those in whom hearing loss is associated with other neurologic complications (table). Although there are insufficient cases to yield a significant statistical conclusion, the data presented in the table suggest that, in the absence of tinnitus, the milder the intensity and the lower the impaired frequencies, the better is the likelihood of recovery.

Although SHL is rarely caused by EBV, physicians should be aware of this rare complication of EBV infection.

Final diagnosis

Sudden hearing loss associated with Epstein-Barr virus infection.

Keywords: hearing loss; Epstein-Barr virus.

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