Skeletal dysplasia with unusual visceral manifestations

Q1: What is the diagnosis?
The diagnosis is pycnodysostosis, which is a rare form of skeletal dysplasia characterised by moderate and generalised osteosclerosis. The diagnosis is based on clinical features and radiological findings. The cardinal features are short stature, large open fontanelles (the fontanelles may remain open even in adulthood), an obtuse mandibular angle, dysplastic clavicles and apex of the thoracic cage, hypoplasia/aplasia of phalanges. Radiography of the bones shows generalised and uniform hyperdensity and marked obliteration of the medullary cavity.

Q2: What is the most important differential diagnosis?
The most important differential diagnosis is osteopetrosis tarda, which is also called Albers-Schonberg disease. This disorder is characterised by severe generalised osteosclerosis, anaemia due to bone marrow failure, and hepatosplenomegaly due to extramedullary erythropoiesis. Neurological deficits like deafness, blindness, and cranial nerve palsies are common, due to bony sclerosis. Radiography of the bones shows no medullary cavity. But short stature, open fontanelles, clavicular dysplasia, and distal phalangeal hypoplasia/aplasia are not seen in osteopetrosis tarda.

Q3: What complications can be anticipated in this case?
In most cases of pycnodysostosis there is adequate bone marrow function with no anaemia or hepatosplenomegaly. The life span is normal. But this case has atypical features that are usually seen in osteopetrosis tarda. These atypical features—namely, anaemia, splenomegaly, and papilloedema—will require close clinical monitoring. The anticipated complications are bone marrow failure, hypersplenism, and optic atrophy. Also other neurological deficits due to ongoing bony sclerosis like deafness and cranial nerve palsies are to be watched for. Lastly, the child may develop transverse bone fractures and obstructive sleep apnoea, which are known complications in a typical case of pycnodysostosis.

Discussion
Pycnodysostosis was first described by Maroteaux and Lamy in 1962. The word pycnodysostosis is of Greek origin (‘pycno’ means dense or thick, ‘dyss’ means defective and ‘ostosis’ means bone). The inheritance of pycnodysostosis is believed to be autosomal recessive. The diagnosis rests on clinical and radiological features.2 3 The exact incidence of pycnodysostosis is not known. Until 1988, 78 cases had been reported.4 The reported male to female ratio is 1:1. The characteristic features of this rare syndrome include short stature, a large head with open fontanelles (often remaining open in adulthood), separated sutures, an obtuse or absent mandibular angle, under developed facial bones, dysplastic clavicles, and hypoplasia or aplasia of distal phalanges.2 3 5 The osteosclerosis of distal phalanges may progressively become more severe. The teeth are malformed, hypoplastic, malpositioned and prone to caries. Deciduous teeth may persist into adulthood giving rise to a double row of teeth. Trunk deformities like kyphosis, scoliosis, and a narrow chest may be seen. There is a tendency for long transverse fractures with minimal trauma in the long bones of lower limbs, metatarsals, clavicles, and mandible. These fractures can occur at any age, are usually self limited, but may lead to deformities. Other features include cranial nerve palsies, a long uvula, obstructive sleep apnoea, and a blue sclera. Most cases have a normal intelligence.6 7 The most consistent radiological feature is moderate generalised osteosclerosis. The osteosclerosis in long bones is most prominent proximally.8

A close differential diagnosis of pycnodysostosis is osteopetrosis tarda (Albers-Schonberg disease) or the benign dominant variety of osteopetrosis, but there are distinct differentiating features. Osteopetrosis tarda occurs in 1:100 000 live births; the reported male:female ratio is 1:1.7 In osteopetrosis tarda, the inheritance is autosomal dominant in most cases and autosomal recessive in a few; also stunt growth and open fontanelles, clavicular dysplasia, and distal phalan-geal hypoplasia are not seen.6 Osteopetrosis tarda is characterised by progressive obliteration of the bone marrow due to formation of new bone, as there is failure of osteoclasts to resorb bone matrix. Progressive anaemia due to bone marrow failure and splenomegaly due to extramedullary erythropoiesis are common findings. Hypersplenism may ensue, leading to pancytopenia. 8 Leucocytoblastosis is found with crowding of cells out of the marrow prematurely (myelophthisis). Deafness, blindness, and neurological deficits due to bony sclerosis are common.9 There is hypotubulation of the ends of shafts of bones with alternating lines of increased and decreased bone density; a finding never found in pycnodysostosis.

It was earlier believed that pycnodysostosis is not associated with anaemia and splenomegaly.10 However a few cases of pycnodysostosis with visceral and haematological manifestations have been described.3 7 11

The child reported here had classical clinical and radiological findings of pycnodysostosis along with atypical features like splenomegaly, anaemia, and thrombocyto-penia. These atypical features are common in osteopetrosis tarda. The boy also had bilateral papilloedema, which has not been reported earlier in association with pycnodysostosis. Thus our case is a link between pycnodysostosis and osteopetrosis tarda indicating that these two disorders are related to each other in a manner more complex than the morphological similarity of increased bone density. Our case is an example of phenotypic heterogeneity in metabolic diseases.

The atypical features in our case warrant follow up for bone marrow failure, hypersplenism, and decreased visual acuity.

Final diagnosis
Pycnodysostosis with splenomegaly, myelophthisic anaemia, and papilloedema.

References

Complications associated with influenza infection

Q1: What do the chest radiograph (fig 1B) and computed tomogram of the thorax (fig 1C; see p 100) show and how would the clinical and radiological findings be best treated?
The chest radiograph on admission (fig 1A) showed right middle lobe consolidation. The second chest radiograph taken six days later (fig 1B) shows that bilateral cavitating masses have developed. These were confirmed by computed tomography to be multiple lung abscesses (fig 1C), the largest of which was 10 x 8 cm in the left lower lobe.

Lung abscesses are areas of suppuration and necrosis with subsequent cavity formation. An air-fluid level is seen radiologically. They can occur in previously normal lung.

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Learning points

- Pycnodysostosis is a rare genetic disorder of the skeletal system characterised by generalised osteosclerosis. The common clinical features are short stature, open cranial fontanelles, an obtuse mandibular angle, dysplastic clavicles, and short stubby hands and feet.
- Osteopetrosis tarda (Albers-Schonberg disease) is another rare genetic disorder characterised by osteosclerosis. Anaemia, splenomegaly, and neurological deficits like deafness and cranial nerve palsies are common findings.
- Pycnodysostosis can rarely have visceral manifestations like anaemia, splenomegaly, and neurological deficits like papilloedema.
- Pycnodysostosis and osteopetrosis tarda are linked to each other in a manner more complex than the morphological similarity of increased bone density.

SELF ASSESSMENT ANSWERS

They are often found after aspiration pneumonia or bronchial obstruction, due to either a foreign body or malignant lesion, but can occur in cases of primary pulmonary infection with Klebsiella pneumoniae or Nocardia asteroides, in cases of septicaemia with Streptococcus Milleri, or as a result of lococele metastases in cases of Staphylococcus aureus septicaemia.

It is unusual for S pneumoniae pulmonary infection to cause a primary lung abscess. More commonly it causes an empyema, which is pus within the pleural cavity requiring drainage.

Lung abscesses should be initially treated conservatively with antibiotics and intensive chest physiotherapy to facilitate drainage. At more than 90% of lung abscesses will be caused at least in part by anaerobic bacteria, antibiotic treatment should include metronidazole, as well as aerobic organism cover, such as a penicillin or cephalosporin.

Antibiotics should be given to all patients, whatever the causative organism. This treatment should be initially intravenous, until the patient can tolerate oral medication and the patient clinically begins to improve. This will usually take about four to eight days. Antibiotics are then given orally for a further six to eight weeks, until the chest radiograph has cleared completely, or abscess cavities become small and stable.

Lung abscesses should not be treated surgically initially, unless there are complications with massive haemoptysis, empyema, or bronchopulmonary fistula. Ten per cent of patients are found to be unresponsive to medical therapy and may require surgical drainage of the abscess.

Failure of medical treatment is associated with abscess cavities of greater than 6 cm, abscesses associated with an obstructing lesion, recurrent aspiration pneumonia, development of an empyema, or prolonged symptomatic complex before presentation.

Primary lung abscesses often become colonised by P aeruginosa. This is found in the oropharynx of debilitated patients, where it is a commensal organism, often along with Proteus species and K pneumoniae. They require combination antibiotics along with treatment of the underlying condition.

This man’s chest radiograph returned to normal after one month with medical treatment alone.

Q2: Is the high influenza A titre relevant to this case?
It is well documented that influenza A infection can predispose an individual to subsequent respiratory tract infection, which often results in pneumonia. This may be caused by the influenza virus itself or by secondary infection due to Streptococcus pneumoniae, S aureus, or Haemophilus influenzae. All can cause considerable mortality and morbidity, even in the young and previously healthy.

Q3: What is the cause of his acute renal failure?
He had acute tubular necrosis causing his acute renal failure. This was due to the haemodynamic disturbance caused by septicaemia. This man became dialysis independent almost one month after his original presentation.

Q4: What is the cause of his abnormal liver function tests?
In cases of S pneumoniae pulmonary infections, there may be associated jaundice around day 4 to 5. The exact cause of this is unknown, but it is often associated with right lower lobe consolidation. It is unusual for bilirubin to rise above 100 µmol/l and the other liver function tests are usually normal.

Final diagnosis
Influenza with secondary S pneumoniae pneumonia and acute renal failure.

References

An atypical case of periodic paralysis
Q1: What is the diagnosis?
Episodic weakness beginning after age 25 is almost never due to primary periodic paralysis. Furthermore, the absence of a similar family history raises a strong suspicion of a secondary disorder rather than the primary form. Tachycardia and a wide pulse pressure in a nervous individual are suggestive of thyrotoxicosis, which can precipitate hypokalaemic and periodic paralysis by enhancing Na+–K+ ATPase activity. The most likely diagnosis, therefore, is hypokalaemic periodic paralysis secondary to thyrotoxicosis.

Q2: How did we confirm it?
Thyroid function tests confirmed the thyrotoxicosis of any cause, and the thyrotoxicosis may be clinically mild.

Q3: How should the patient be managed?
Treatment is that of thyrotoxicosis. The attacks cease when the euthyroid state is restored.

Discussion
Thyrotoxic periodic paralysis is six times more common in males than in females. It is particularly common in males with thyrotoxicosis of any cause, and the thyrotoxicosis may be clinically mild. The episodes of muscle weakness are invariably associated with a decrease in serum potassium concentration, although it may not always be subnormal. Hypokalaemia alone is not the only cause because potassium levels sufficient to provoke paralysis in a thyrotoxic patient has no effect when the same patient is euthyroid. The exact cause of susceptibility of some thyrotoxic patients to periodic paralysis is not known. Whatever the mechanism, the attacks cease in all patients when the euthyroid state is restored. Therefore, it is important that clinicians consider the diagnosis of thyrotoxicosis in any patient with atypical hypokalaemic periodic paralysis.

Final diagnosis
Hypokalaemic periodic paralysis secondary to thyrotoxicosis.

References

Swollen and stiff shoulder
Q1: What are the pathological changes seen in the radiograph (see p 101)?
The radiograph shows destruction of proximal humerus and glenoid with joint effusion and no periosteal reaction. Neuropathic joint is one of the conditions in which such radiographic appearances are seen (box 1).

Q2: What are the pathological changes seen in the MRI scan (see p 101)?
The MRI scan shows Arnold-Chiari malformation with the herniation of cerebellum and brainstem with thinning of the pons and medulla.
medulla in the cervical canal region. A combination of central nervous pathology with bone destruction is consistent with neuropathic joint (Charcot’s joint).

Discussion

Charcot’s joint or neuropathic joint has been described as a disorganised and relatively painless joint. There are a number of causes of this condition (box 2) but no consensus regarding the pathogenesis. The neurotraumatic theory suggests that the changes result from repeated mechanical trauma to a joint that is insensitive to pain. The neurovascular theory proposes that the changes result from a neurally initiated vascular reflex that leads to hyperaemia and active bone resorption by osteoclasts. Forty years back, 90% of neurovascular neuropathic arthropathies were related to tabes dorsalis, the remaining being distributed among the other disease entities. With the control of syphilis, diabetes mellitus and syringomyelia now account for a substantially larger proportion of Charcot’s joints. Different aetiologies have predisposition to affect different joints in the body (box 3). Presently it is most commonly seen in the midfoot and forefoot of diabetic patients.

Pain is most often the presenting feature, though it is not commensurate with the severity of the joint destruction. Some patients have no pain in the affected joints. Pain often increases with spontaneous fractures and dislocations. The joint is distended due to the effusion and synovitis. It is not inflammatory in nature, though in calcium pyrophosphate dihydrate crystal deposition disease it can be inflammatory. It may even be bloody or xanthochromic in nature at times.6

Radiographs show changes similar to those of osteoarthritis in the initial stages. But later on there is subluxation, fragmentation, and proliferation of bone with lot of debris in the joint. The bone destruction and joint disorganisation seen in radiographs should be distinguished from other causes of osteolysis (box 1). Bone scan shows increased uptake even in early disease. Pathological changes are similar to those of osteoarthritis but there is active pannus formation in Charcot’s joints. Often the infection in these joints is difficult to diagnose. Delay in diagnosis of neuropathic joint is fairly common.3

Neuropathic shoulder is relatively a rare disorder and Arnold-Chiari malformation is an exceptionally rare cause of Charcot’s joint. This is probably the fourth case of Charcot’s shoulder due to Arnold-Chiari malformation.2

Treatment requires the management of the underlying condition if possible and the control of infection of the joint if present. Patient education has a major role in the management. They have to be taught regarding the use of protective footwear, braces, a cane, and immobilisation. Arthrodesis can be performed for unstable joints, though it is difficult and requires resection of great amount of bone. Total joint replacement is also not recommended because of lack of capsuloligamentous support, though they have been performed in hip and knee with success in 3–7 years follow up.5

Final diagnosis

Charcot’s arthropathy of shoulder due to Arnold-Chiari malformation.

References


A woman with dysphagia and Raynaud’s phenomenon

Q1: Comment on the appearance of her tongue (fig 1) face (figs 3 and 4), and hands (fig 5) (see p 102–103)

Figure 1 reveals florid telangiectasias affecting the buccal mucosa and tongue. Figures 3 and 4 reveals facial telangiectasias and perioral radial furrowing. Figure 5 shows taught shiny skin and acrocyanosis of the digits.

Q2: Comment on the appearance of her barium swallow (fig 2) and suggest a unifying diagnosis

The barium swallow (see p 102) shows moderate oesophageal dilatation with no evidence of active peristalsis, suggesting a motility disorder. The underlying diagnosis is CREST syndrome (see discussion below).

Q3: Examination of her left elbow revealed a hard nodule over the extensor aspect. What does the radiograph (fig 6) show?

The radiograph of the elbow (see p 103) illustrates extensive subcutaneous calcification.

Discussion

Scleroderma is a generic term describing a group of related connective tissue diseases characterised by the development of skin organ fibrosis, Raynaud’s phenomenon, and specific autoantibodies in sera. A working classification normally divides these diseases into systemic and localised cutaneous forms. Localised cutaneous forms include morphea, linear scleroderma, and en coup de sabre (linear sclerotic lesion often affecting the calvarium).

Systemic forms include two main disease patterns. First, limited cutaneous systemic sclerosis where skin sclerosis is restricted to the extremities and face; CREST (Calcinosis, Raynaud’s phenomenon, eScleroderma, dysmotility, Sclerodactyly, and Telangiectasia) syndrome is a subset of this group. Although limited forms have prominent vascular instability characterised by severe Raynaud’s phenomenon and pulmonary hypertension, internal organ fibrosis is uncommon compared with the diffuse disease pattern group and this is reflected in an overall 10 year survival of around 75%. Patients in this group often have a long history (up to 15 years) of Raynaud’s phenomenon before the development of sclerodactyly, facial disfigurement, etc.

The second disease pattern is the diffuse cutaneous systemic sclerosis group; this group represents the most serious form of the condition. These patients typically have a very short history of Raynaud’s phenomenon before constitutional symptoms, skin oedema (then sclerosis), and internal organ involvement become apparent. The latter may manifest in the respiratory system (pulmonary fibrosis), genitourinary system (hypertensive renal crisis), cardiovascular system (cardiovascular conductive defects, restrictive myocardopathy), or gastrointestinal tract (malabsorption, bacterial overgrowth).

An interesting clinical problem which can often present to the practising physician or general practitioner alike is that of a young

Self assessment answers 109

1. Neural abnormality
   - Tabs dorsalis.
   - Syringomyelia.
   - Meningocele.
   - Spinal cord trauma.
   - Multiple sclerosis.
   - Paraplegia.
   - Arachnoiditis.
   - Adhesive arachnoiditis.
   - Arnold-Chiari malformation.
   - Charcot-Marie-Tooth disease.
   - Alcoholic neuropathy.
   - Leprosy.
   - Myelopathy of pernicious anaemia.
   - Congenital insensitivity to pain.
   - Familial amyloid neuropathy.
   - Non-familial amyloid neuropathy in dialysis patients.
   - Familial dysautonomia.

2. Endocrine pathology
   - Diabetes mellitus.
   - Acromegaly.
   - Familial dysautonomia.
   - Familial amyloid neuropathy.
   - Myelopathy of pernicious anaemia.
   - Leprosy.
   - Tabes dorsalis.
   - Hip.
   - Knee.
   - Spine.
   - Shoulder.
   - Elbow.
   - Ankle joint.
   - Tarsal and metatarsal joints.

3. Infections
   - Leprosy.
   - Yaws.

4. Drugs
   - Thalidomide.
   - Intracutaneous steroids.

5. Others
   - Calcium pyrophosphate dihydrate crystal deposition.
   - Amyloidosis associated with Waldenstrom’s macroglobulina.
   - Chronic haemodialysis.
   - Juvenile rheumatoid arthritis.
   - Scleroderma (with cervical osteolysis).

Box 2: Causes of neuropathic joints

Box 3: Joints frequently involved in different conditions

1. Diabetes mellitus
   - Tarsal and metatarsal joints.
   - Ankle joint.

2. Tabs dorsalis
   - Knee.
   - Hip.
   - Spine.

3. Syringomyelia
   - Shoulder.
   - Elbow.
   - Cervical spine.

4. Calcium pyrophosphate dihydrate crystal deposition
   - Knee.
   - Hip.
woman (of about 20 years) presenting with Raynaud-like symptoms. Is it an idiopathic isolated pathology with a benign course (Raynaud’s disease) or is it the forerunner of a potentially life-threatening underlying connective tissue disorder (Raynaud’s phenomenon)? Although no specific test can provide the answer, by searching for specific features in the history, on examination and at the laboratory, one can often reassess the patient or alternatively arrange long term outpatient follow up (see box 1).

It is worthwhile elaborating on the gastrointestinal manifestations of the scleroderma cohort of patients, especially in view of the presentation of the case described above. Oesophageal dysmotility is by far the commonest manifestation in the gut and presents clinically with heartburn, dysphagia, and odynophagia. Later manifestations include bleeding, stricture, Barrett’s oesophagus, and finally adenocarcinoma of the distal oesophagus. At a histological level, distal oesophageal biopsies reveal smooth muscle atrophy coupled with submucosal fibrosis. Endoscopy with biopsy, barium studies, and manometry all have a place in the diagnostic process. Management may be medical (proton pump inhibitors) or surgical (fundoplication).

Small and large bowel involvement is also seen and again is a result of muscle atrophy and fibrosis causing dysmotility, stasis and bacterial overgrowth. Patients complain of colic, bloating, diarrhoea, and even steatorrhoea with small intestinal disease. Breath tests and duodenal aspirates at endoscopy help to identify bacterial overgrowth which may be amenable to oral broad spectrum antimicrobial therapy. Colonic disease is rarely clinically significant and predominantly causes constipation.

It is worth noting that primary biliary cirrhosis (PBC) is a recognised association of scleroderma subsets with good prognosis. Other staging investigations will depend on the clinical features present. For example, pulmonary function testing, high resolution computed tomography of chest and echo-cardiography for those complaining of breathlessness (7pulmonary fibrosis, 7pulmonary hypertension).

There is no curative treatment for systemic sclerosis but the majority of patients can be helped with an organ based approach to the complications which arise (see box 2).

No drug has been shown to halt the progression of systemic sclerosis in a sufficiently large and powerful prospective randomised controlled clinical trial. Ascertaining improvement or deterioration in scleroderma is difficult. Moreover, the disease is variable in severity and rate of progression. Also, spontaneous improvement may occur after several years, especially involving the skin. Thus trials are difficult to design and interpret in the context of systemic sclerosis. Suggested treatments to halt the fibrotic process include D-penicillamine and gamma interferon, but efficacy remains to be proven in a randomised trial setting. In addition, it may not be justifiable to use treatments with potentially serious side effects in some scleroderma subgroups with good prognoses (for example, limited cutaneous disease) especially given the lack of proved efficacy.

Final diagnosis
CREST syndrome.

References

An unusual case of chronic renal failure

Q1: What does the MRI scan show (see p 104)?

The MRI scan of the brain shows generalised cerebral and cerebellar atrophy. There is a quite extensive abnormal high signal on the T2-weighted images and fluid attenuated inversion recovery (FLAIR) sequence in both the cerebral hemispheres, pons, and in the cerebral white matter involving both peri-ventricular and subcortical areas. These appearances are not specific but are likely to be due to widespread ischaemic changes.

Q2: What is shown in fig 3 (see p 104)?

Angiokeratomas. These are vascular lesions of the skin, which usually appear at puberty, increase with age, and are mainly confined to the bathing trunk area. These occur as a result of ectatic dilatation of the blood vessels weakened by endothelial deposition of ceramide.

Q3: What is the diagnosis?

Fabry’s disease.

Q4: What do you expect to see in the electron microscopic examination of the kidney?

Multilamellar bodies (zebra bodies).

Q5: What investigation will you do to confirm the diagnosis?

The α-galactosidase levels should be measured as they are diagnostic. In our patient the α-galactosidase levels were undetectable.

Discussion

Fabry’s disease is a rare (1:40,000) X linked recessive disorder in which partial or total deficiency of lysosomal α-galactosidase results in the progressive accumulation of glycolipids in various tissues including the kidney. The single most debilitating symptom of Fabry’s disease is the pain. The painful crises most often begin in childhood and consist of agonising burning pain initially in the palms and soles which often radiates to the proximal extremities and other parts of the body. Cardiac manifestations include anginal chest pain, myocardial ischaemia, and infarction, congestive cardiac failure, and cardiac enlargement. The electrocardiogram may show left ventricular hypertrophy, ST segment changes, and T wave inversion. Short PR intervals have been reported. Cerebrovascular manifestations result primarily from multifocal small vessel involvement and may include personality changes, psychotic behaviour, thrombosis, seizures, aphasia, hemiplegia, etc. Progressive glycopigment deposition in the kidney results in proteinuria and other signs of renal impairment with gradual deterioration of renal function and development.

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of azotaemia in middle age. Ocular involvement is most prominent in the cornea (opacities), lens (cataract), conjunctiva, and retina (vascular lesions). Other clinical features include lymphoedema, episodic diarrhoea, avascular necrosis of the head of femur, delayed puberty, fine facial and body hair, dyspnoea, and wheezing respiration. Treatment of patients with regard to cardiac, pulmonary, and central nervous system manifestations is non-specific and symptomatic. Since renal insufficiency is the most frequent late complication in patients with this disease, chronic haemodialysis and/or renal transplantation have become life saving. At present the most practical and effective therapy is preventive screening of all suspect heterozygotes, genetic counselling, and prenatal diagnostic studies should be made available to all at risk families. Enzyme replacement has been shown to be beneficial over short term in small studies. With recent developments in molecular genetics it is possible to produce the human recombinant enzyme α-galactosidase. In addition the results of a trial of gene therapy in a Fabry’s disease gene knockout mouse appear promising.

Final diagnosis

Fabry’s disease.

References

A case of cough and dysphagia

Q1: What abnormalities are seen on the computed tomogram (fig 1; see p 104) and on views of the right main bronchus at bronchoscopy (fig 2; see p 105)?

The computed tomogram shows the presence of a large fistula between the right main bronchus and oesophagus, with resultant areas of shadowing seen in both lungs due to aspiration. At bronchoscopy, the oesophagus containing the nasogastric tube can be visualised through the fistula.

Q2: What is the most likely cause of these appearances?

The most likely cause of these appearances is a malignant broncho-oesophageal fistula. Oesophageal biopsies confirmed adenocarcinoma.

Q3: What other conditions may cause similar appearances?

Non-malignant causes of oesophago-respiratory fistula include congenital lesions, infection, and trauma.

Q4: What treatment options are available?

Possible treatment modalities include:
- Insertion of oesophageal stent.
- Endoscopic oversewing.
- Oesophageal bypass.
- Oesophageal exclusion.
- Chemo/radiotherapy.
- Supportive therapy.

Discussion

Malignant oesophago-respiratory fistula is estimated to develop in 45% and 0.3% of all primary oesophageal and bronchial carcinomas respectively. It is associated with a dismal prognosis, with a median survival for untreated cases of between one to six weeks. Typical features include cough, which is worse on swallowing (Ono’s sign), aspiration, fever, dysphagia, and pneumonia. Appropriate investigations include bronchoscopy, oesophagoscopy and contrast radiography, although all may be misleadingly normal. Initial management is primarily aimed at reducing pulmonary contamination from the fistula, and should be started as soon as possible after diagnosis, as delay is associated with exponential increase in early mortality. Immediate treatment includes keeping the patient nil by mouth, and providing general supportive therapy, including broad spectrum antibiotics where appropriate. Insertion of an oesophageal stent, which occludes the opening of the fistula, is generally effective in preventing pulmonary aspiration, but may be complicated by bleeding, migration, oesophageal obstruction, and perforation. Surgical techniques, including oesophageal exclusion or by-pass, are associated with high operative mortality, but result in effective symptomatic palliation in survivors. Congenital oesophago-respiratory fistulae generally present in early childhood, although they are occasionally not diagnosed until adult life. Other reported causes of fistula include tuberculosis, and herpes virus infection, chest trauma, and pressure necrosis from tracheal cuff after prolonged ventilation. Surgical repair is generally required for non-malignant oesophago-respiratory fistulae, but lesions may be amenable to less invasive techniques, including closure with fibrin glue applied via the bronchoscope.

Final diagnosis

Oesophageal carcinoma resulting in broncho-oesophageal fistula and bronchopneumonia.

References

An elderly lady with collapse

Q1: What are the findings in figs 1a and 2 (see p 105)?

Figure 1 shows right sided partial ptosis and a divergent squint due to pupil sparing third nerve (oculomotor) palsy—that is, there is no pupil asymmetry. In fig 2, the patient was asked to raise both arms and it shows weakness of the left arm in comparison with the right arm. Indeed the patient had left hemiparesis. The right arm, however, is not fully raised probably due to a degree of proximal weakness. Figure 2 also shows a feeding pump next to the patient and a feeding tube looped over the back of her chair leading to her percutaneous endoscopic gastrostomy (PEG).

Q2: What is the diagnosis?

CROSSED HEMIPLEGIA A DISEASE AFFECTING THE RIGHT MID-BRAIN INVOLVING THE RIGHT THIRD NERVE AND THE CORTICOSPINAL TRACT AT THE LEVEL OF THE CEREBRAL PEDUNCLES

Computed tomography of the brain did not reveal any evidence of bleed, but a low density area in the left occipital lobe. The left hemiplegia gradually improved but dysphagia persisted requiring insertion of a PEG for feeding. Eventually the patient was discharged to a residential home. Six months after the onset, she remains with a residual hemiparesis, partial third nerve palsy, and PEG feeding.

Discussion

Clinical features of the third, fourth, and sixth cranial nerve palsy

The third nerve supplies all the extraocular muscles of the eye except the lateral rectus muscle which is supplied by the sixth (abducens) nerve, and the superior oblique muscle being innervated by the fourth (trochlear) nerve. The features of complete third nerve palsy include ptosis, divergent squint, diplopia, fixed dilatation of the pupil, and paralysis of accommodation. Patients with third nerve palsy are often relatively asymmetrical because of the ptosis, but on raising the eyelid, they would have diplopia in all directions except on lateral gaze to the side of the lesion.

However when the fourth nerve palsy develops, it often leads to a very subtle diplopia that is worse when the head is turned and away such as when descending the stairs. This abnormality results because of a failure of extorion leading to an unopposed pull of the inferior rectus which raises the eye. Consequently patients slightly tilt the head and in children this sometimes may be felt to mimic a torticollis.

The sixth nerve palsy causes medial (convergent) squint with failure of adduction of the affected eye, and the diplopia persists in all directions.

The third nerve nucleus and its relations

The third nerve nucleus in the mid-brain has two components: the third nerve motor nucleus and the Edinger-Westphal. The third nerve nucleus has such a long vertical extent that damage at various points can often lead to incomplete lesions. The third nerve motor nucleus is situated in the lower mid-brain and gives rise to the motor fibres supplying the extraocular muscles as mentioned earlier.

The Edinger-Westphal nucleus is situated adjacent to the third nerve motor nucleus, and receives fibres from the periaqueductal grey matter involved in the consensual light reflex as well as information from the adjacent third nerve nucleus mass which is activated when the medial rectus muscle is activated in accommodation. The Edinger-Westphal nucleus gives rise to the preganglionic parasympathetic fibres.

The third nerve emerges from the mid-brain between the cerebral peduncles where the corticospinal tracts are carried, and at this point it
lies between the posterior cerebral artery and superior cerebellar artery and then it runs paral-
lel to the posterior communicating artery until it reaches the cavernous sinus. After
entering the orbit through the superior orbital fissure, the third nerve divides into an upper
and lower branch. The upper branch supplies the levator palpebrae superioris and superior
rectus muscles. The lower branch supplies three muscles: the medial rectus, the inferior rectus,
and the inferior oblique muscle.

The nerve to the inferior oblique muscle conveys the preganglionic parasympathetic fibres
to the ciliary ganglion from which the parasympathetic fibres then subdivide into 8–10 cranial nerves supplying
the pupilloconstrictor muscles.

The pupilloconstrictor fibres and those innervating the levator palpebrae lie in a
superficial and dorsal position on the nerve relaying in the ciliary ganglion which is in the position of the extreme of this anatomical
characteristic, a fixed dilated pupil is often the first sign of third nerve (oculomotor) com-
pression and piosis the second, before the external ophthalmoplegia develops.

The part of the parasympathetic fibres of the third nerve nucleus are the pupilloconstrictor fibres which lie closer to the midline, are more
affected by pathological processes. The nasal fibres, which lie closer to the midline, are more vulnerable to compression by enlargement of the
pituitary gland, causing an ipsilateral temporal visual field defect. This phenomenon, which is of great value in topographical diagnosis, was
first pointed out by Traquair and hence this visual field defect is known as the junctional
scotoma of Traquair. In some instances, the defect may be confined to the paracentral
region alone. The earliest detectable sign of visual field defects of chiasmal origin is
desaturation of the red colour of a pin as it is moved from the nasal into the temporal field
(temporal desaturation).

Q3: What further investigations should be performed?

The structure and function of the pituitary gland may be assessed by imaging (preferably with magnetic resonance imaging, MRI) and
specific blood tests respectively. MRI of the pituitary region (fig 1 above) showed a large
mass lesion arising from the pituitary fossa, the bony walls of which showed some erosion,
and extending above the sella turcica to the right of the midline. Coronal sections showed
that the tumour selectively compressed the left optic nerve just at its point of entry into
the chiasm (fig 1 above, arrow). The lesion showed marked enhancement with intra-
venous contrast (gadolinium).

Tests of pituitary function revealed a greatly increased prolactin level (>160 000 mIU/l),
indicating that the lesion was a giant prolac-
tinoma. Retrospectively, it was noted that the patient had been increasingly lethargic and
sleepy, with reduced energy and facial hair,
but there was no history of galactorrhoea. He was treated with the long acting dopamine
agonist cabergoline (0.5 mg/week), and fol-
lowed up in the pituitary clinic with monitor-
ing of visual fields, prolactin levels, and
tumour size. After six months his visual
symptoms had resolved, prolactin level had
fallen, and there was considerable shrinkage of the tumour on repeat MRI.

A developing visual field defect

Q1: What is the visual field defect (fig 1; see p 106)?

Left temporal hemifield defect.

Q2: What is the neuroanatomical correlate of this clinical finding?

Non-congruent (heteronymous) hemianopic
defects usually suggest a lesion in the chiasmal
region. A unilateral temporal hemifield defect,
as seen here, suggests a prechiasmal lesion,
situated at the point where the optic nerve joins
the chiasm (the anterior angle of the chiasm).

Discussion

Although bitemporal hemianopia is the com-
monest visual field defect detected in patients
with pituitary adenoma, the junctional
scotoma of Traquair has been found in 1–10% of cases in large series (which predate computed tomography and MRI).

This visual field defect may also occur
occasionally in the context of other pathologies, such as meningioma, aneurysm, and craniopharyngioma.

Traquair also described another type of junctional scotoma, which, although it produces a quite different clinical picture, may be a possible source of confusion with the aforementioned type. Involvement of the crossing and ventral nasal retinal fibres as they loop anteriorly into the contralateral optic nerve (Wilbrand’s knee) produces a contralateral upper temporal scotoma, along with a visual field defect (central scotoma) in the ipsilateral eye; because the latter dominates the clinical picture, the former is easily missed. This “junctional scotoma”, so called to differentiate it from the junctional scotoma of Traquair, is usually due to intrinsic optic nerve pathology, but it has also been reported in association with a pituitary adenoma.

Final diagnosis
Giant pituitary prolactinoma causing junctional scotoma of Traquair.

Learning points
- There are two types of junctional scotoma, both of clinicoanatomical localising value.
- The junctional scotoma of Traquair is an ipsilateral temporal field defect with midline hemianopic character, resulting from involvement of crossing nasal fibres at the anterior angle of the chiasm.
- The junctional scotoma is an easily overlooked contralateral superior temporal scotoma associated with ipsilateral optic neuropathy, resulting from lesions of the optic nerve just anterior to the chiasm which damage the crossing ventral nasal fibres looping into the optic nerve (Wilbrand’s knee).
- Large pituitary tumours may be associated with subtle neuro-ophthalmological signs, emphasising the importance of careful clinical examination of the visual fields.

References
A woman with dysphagia and Raynaud's phenomenon

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