An unusual electrocardiographic abnormality

Q1: What is shown in fig 1 (see p 539), and what is its significance?

Figure 1 shows a prolonged QT interval (corrected QT 520 milliseconds) and macroscopic T wave alternans. T wave alternans is defined as a beat to beat variation in the amplitude or polarity of the T wave. Macroscopic T wave alternans is a predictor of malignant ventricular arrhythmias. Microvolt T wave alternans is a validated predictor of mortality and morbidity in a variety of patient groups. This ECG anomaly is seen with both transient physiological stress (for example, exercise), and with pathological stress such as electrolyte abnormalities and myocardial ischaemia. Indeed, revascularisation in ischaemia has even been shown to reduce the incidence of T wave alternans. It has also been documented in association with the long QT and Brugada syndromes.

T wave alternans on a millivolt scale visible to the naked eye (macroscopic T wave alternans) is predominantly a subject for individual case reports. It is often a precursor to the subsequent development of torsades de points (polymorphic ventricular tachycardia). Regardless of amplitude, T wave alternans should be regarded as a warning of malignant arrhythmias.

Q2: What is the arrhythmia in fig 2 (see p 539)?

The upper trace in fig 2 is lead II from a conventional electrocardiographic recording. It shows macroscopic T wave alternans in the first four beats degenerating into torsades de points (polymorphic ventricular tachycardia). In comparison with fig 1, the QT interval is yet further prolonged. The lower trace shows loss of the arterial pressure waveform.

Q3: What was the procedure used to treat the patient in fig 3 (see p 539)?

Figure 3 shows a ventricular paced rhythm. Torsades de points in this patient was treated by a temporary ventricular pacing. The patient was given verapamil to ensure his own rhythm was slower than that delivered by the temporary pacing wire. In addition, the patient received intravenous magnesium sulphate to correct the hypomagnesaemia.

Discussion

T wave alternans is uncommon and often overlooked except when it is of a large (millivolt) amplitude such as in this case. Its mechanism demonstrates modern electrophysiological understanding of the basis of arrhythmia generation. Many arrhythmias occur as a result of re-entry circuits. A re-entry circuit occurs when a depolarising wave travels in a circle from myocyte to myocyte. Each myocyte becomes refractory for a short time to further depolarisation as the ion channels in the cell membrane are reset. By the time the wave comes full circle, however, the first myocyte is no longer refractory and is able allow the circuit movement to continue round the circuit indefinitely.

Some circuits depend on heterogeneity of repolarisation. Normally the myocardium depolarises rapidly and synchronously which is represented on the ECG by the narrow QRS complex. The myocardium is then refractory until ventricular repolarisation is completed. Repolarisation is slower and more heterogeneous than depolarisation and hence the T wave appears as broad deflection on the ECG. The more heterogeneous the repolarisation, the greater the chance that part of the myocardium will no longer be refractory should an ectopic trigger be present, and hence allow a re-entry circuit to be established.

Heterogeneity of repolarisation is formally known as transmural dispersion of repolarisation (TDR). Increased TDR occurs with electrolyte abnormalities (for example, hypokalaemia, hypomagnesaemia), with intrinsic abnormalities of the ion channels due to genetic mutations (the congenital long QT syndromes), and as an effect of drug therapy (antiarrhythmics, β-agonists, erythromycin, etc.).

Increased TDR manifests on the surface electrocardiogram as alteration in the timing and amplitude of the T wave. This is the mechanism of both T wave alternans and the better known prolongation of QT interval. Interestingly, while T wave alternans is always associated with increased TDR, long QT intervals may be found with a normal distribution of repolarisation. A long QT interval may occur when the whole myocardium repolarises late but synchronously (small TDR) or when just part of the myocardium lags behind repolarisation of the rest (large TDR). Drugs such as amiodarone prolong the action potential, and hence the QT interval, yet decrease the TDR.

This patient had two separate factors operating to increase the TDR. Firstly he had a low serum magnesium concentration which like abnormalities in potassium and calcium is known to alter the dynamics of repolarisation of the myocardium. Secondly, he was on nebularised β-agonists (salbutamol), and given 1:1000 adrenaline during the cardiac arrest. The dispersion in the rate of repolarisation is therefore increased.

Just as the T waves represent myocardial repolarisation, the T wave alternans is the correlate of increased dispersion in the rate of repolarisation. Sometimes the myocytes repolarise simultaneously and sometimes less so; sometimes the wave of repolarisation is in one direction and sometimes the other. It is an early warning sign of re-entry circuits and ventricular arrhythmias and in particular torsades de points. Although T wave alternans is a rare electrocardiographic sign, when present it should be treated with suitable respect.

Final diagnosis

Macroscopic T wave alternans and recurrent torsades de points.

References


A diagnostic conundrum

Q1: What is the diagnosis in this case?

The diagnosis is Whipple's disease. This is a rare multisystem disorder characterised by weight loss, diarrhoea, abdominal pain, arthralgia and lymphadenopathy, though presentations may be very variable. It is caused by a Gram positive, PAS positive bacillus called Tropheryma whippellii which was identified in 1992.

It has been reported in all age groups, though it is commonest in middle aged white males. Whipple's disease commonly involves the gastrointestinal tract causing a dilated thickened intestine with villous atrophy and malabsorption, resulting in anorexia, weight loss, abdominal pain, anaemia, hypobiuminaemia and rarely, clotting disorders.

The heart and its layers can be affected. Polyarthralgia is common though transient and episodic. Generalised hyperpigmentation can be found in up to 50% of patients. One of the striking features is mesenteric, abdomi- nal, retroperitoneal, mediastinal, and peripheral lymphadenopathy which can often be mistaken for lymphoma, sarcoidosis, or other granulomatous disorders. Ten percent of pa- tients will have neurological involvement at some stage of their illness. Dementia, ophthalmoplegia, and facial myoclonus are the commonest features.

Q2: What is the pathognomonic central nervous system manifestation?

The answer is facial and ocular myoclonus. This includes oculomotoric myorhythmia and oculofacial-skeletal myorhythmia. The former is characterised by a slow, smooth convergent-divergent pendular nystagmus associated with synchronous contractions of the jaw and the latter is associated with contrac- tions of other body parts. These are rare findings present in 20% of patients with central nervous system disease and are as diagnostic as a positive biopsy or a positive polymerase chain reaction assay of the bacterial RNA.

Q3: What is the diagnostic test?

The diagnosis of Whipple's disease requires a high index of clinical suspicion. Routine blood tests are non-specific as are tests of malabsorption. Histopathological examination of biopsies of the organs involved reveal PAS positive macrophages containing clumps of T whippellii. In about 30% of cases this is negative. The current diagnostic test is polymerase chain reaction of bacterial 16S ribosomal RNA from tissue biopsies, cerebrospinal fluid, blood, etc.

Q4: How does one treat this condition?

Current treatment is long term co-trimoxazole (trimethoprim-sulphamethoxazole). Initial treatment in those with neurological involvement is an intravenous combination of cephalosporins and aminoglycosides, followed by oral co-trimoxazole. Locomotor and gastrointestinal symptoms may show improvement in days when histological remission may take 1–2 years. Relapse rates can be up to 35%.

Final diagnosis

Whipple's disease.
Progressive furrowing of skin with digital clubbing

Q1: What is the diagnosis?
The diagnosis is primary hypertrophic osteoarthropathy or pachydermoperiostosis or Touraine-Solente-Gole syndrome. The presence of characteristic facial features with cutis verticis gyrata and advanced clubbing of the digits in the absence of any systemic features suggest the diagnosis. Radiological evidence of periostitis of the involved bones helps in confirmation of the diagnosis.

Q2: What are the radiological findings shown?
The radiograph of wrist (see p 541) shows periostitis, new bone formation around the styloid process of radius. Cortical sclerosis and periosteal thickening are seen along lower ends of the shafts of radius, ulna and metacarpals, proximal and middle phalanges of both hands.

Q3: Which other conditions are to be differentiated clinically from this entity?
This condition has to be differentiated from the secondary form of hypertrophic osteoarthropathy, which occurs in relation to bronchial carcinoma. Rarely, other chronic airway malignancies, suppurative lung diseases, and congenital heart diseases. Here, facial features are minimal or absent and the osteoarthropathy or pachydermoperiostitis is coarser and extends more distally to involve the epiphyses. Involvement of musculoskeletal insertions and interosseous membranes are also seen in the late stage. Calcification of tendons and ligaments is common. These give rise to painful, restricted movement of distal large joints. Soft tissues over wrists and ankles are thickened and associated carpal and tarsal tunnel syndromes are seen. Advanced clubbing of the digits and palmpoplantar hyperhidrosis hampers the daily activities of life. There may be associated anomalies like hypertrophic gastropathy and peptic ulcer disease. 

Q4: What is the cause?
Bilateral simultaneous angle closure glaucoma has been described in association with surgical anesthesia and various drugs including paroxetine, bromocriptine, imipramine, and fluoxetine. Idiopathic bilateral simultaneous angle closure is a very rare entity. Saunders reported a series of 41 patients who presented with acute angle closure and only one had simultaneous bilateral symptoms of unknown cause. Our patient had no obvious cause and the onset of symptoms of bilateral angle closure attack was spontaneous.

Discussion
An acute attack of angle closure glaucoma is normally associated with a very high intraocular pressure along with reduced visual acuity, oedematous cornea, and shallow anterior chamber. The intraocular pressure in this case is low in both eyes because of prolonged attack leading to ciliary body shutdown (shock). The ciliary body shutdown led to reduction in aqueous production and the iritis atropic patches signify prolonged exposure of both eyes to high intraocular pressure.

Q6: How would you manage this patient?
The most important point is to reduce the inflammation so that the antiglaucoma medication can work. The patient was started on prednisolone (0.5%) and pilocarpine (2%) eye drops in both eyes. On further follow up, the corneal oedema resolved and gonioscopy revealed closed anterior chamber angles in both eyes. On her last follow up her visual acuity improved to 6/12 and 6/9 in right and left eye respectively. Later a laser iridotomy was carried out in both the eyes.

Primary hypertrophic osteoarthropathy starts insidiously in childhood or commonly during puberty and is characterised by remarkable cutaneous features, clubbing, and periostitis. Pathogenesis involves abnormalities in collagen synthesis. Fibroblasts from the affected skin are hyperactive with increased synthesis of collagen. Molecular studies reveal evidence of upregulated collagen transcription.

The skin becomes thick and coarse with prominence of the usual lines of facial expression. Thickness of the eyelids gives rise to the impression of ptosis. Seborrhoea, acne, and folliculitis are common. Overgrowth of scalp tissue in relation to underlying skull bone gives rise to cutis verticis gyrata.

Bilateral, symmetrical, distal long bone involvements are seen, initially involving the distal diaphysis of tibia, fibula, radius, ulna, metatarsals, metacarpals, and phalanges. In advanced disease, proximal long bones and flat bones of the pelvic and shoulder girdles may also be involved. There is periostitis giving rise to radiological features of periarticular, irregular new bone formation and cortical thickening. Compared with the secondary form, this is coarser and extends more distally to involve the epiphyses. Involvement of musculoskeletal insertions and interosseous membranes are also seen in the late stage. Calcinosis of tendons and ligaments is common. These give rise to painful, restricted movement of distal large joints. Soft tissues over wrists and ankles are thickened and associated carpal and tarsal tunnel syndromes are seen. Advanced clubbing of the digits and palmpoplantar hyperhidrosis hampers the daily activities of life. There may be associated anomalies like hypertrophic gastropathy and peptic ulcer disease.

Q5: What is the diagnosis?
An acute attack of angle closure glaucoma. A rare entity associated with a very high intraocular pressure along with reduced visual acuity, oedematous cornea, and shallow anterior chamber. The intraocular pressure in this case is low in both eyes because of prolonged attack leading to ciliary body shutdown (shock). The ciliary body shutdown leads to reduction in aqueous production and the iritis atropic patches signify prolonged exposure of both eyes to high intraocular pressure.

Q3: How would you manage this patient?
The most important point is to reduce the inflammation so that the antiglaucoma medication can work. The patient was started on prednisolone (0.5%) and pilocarpine (2%) eye drops in both eyes. On further follow up, the corneal oedema resolved and gonioscopy revealed closed anterior chamber angles in both eyes. On her last follow up her visual acuity improved to 6/12 and 6/9 in right and left eye respectively. Later a laser iridotomy was carried out in both the eyes.

Primary hypertrophic osteoarthropathy is a rare, autosomal dominantly inherited disorder with variable penetrance. It affects males predominantly with a sex ratio of 9:1, and in about one third cases, family history is positive.
Learning points

- Patients with acute angle closure glaucoma may present with systemic symptoms and reduced vision.
- They should be referred urgently to an ophthalmologist to prevent acute morbidity and blindness.
- An acute attack may spontaneously resolve by causing ciliary body shutdown and iris atrophy and thus bringing intracocular pressure back to normal.

Final diagnosis

Diagnosis is bilateral simultaneous acute angle closure glaucoma.

References


An odd case of multiple “cannonball metastases”

Q1: What abnormalities are seen on the radiograph?

The chest radiograph (see p 542) shows evidence of a raised left hemidiaphragm and small left pleural effusion. Two pulmonary nodules, which have no visible calcification or cavitation but well defined margins, are noted overlying the left midzone. One lesion lies adjacent to and above the aortic knob, the other one adjacent to the left heart border. A subsequent contrast enhanced spiral computed tomogram of her chest showed two small focal nodules in the right lobe, two moderate sized in the left upper lobe, and one large mass measuring approximately 6 x 9 x 11 cm replacing most of the left lower lobe, also a small left pleural effusion; there was no lymphadenopathy.

Q2: What is the differential diagnosis?

The differential diagnosis of multiple lung masses is quite complex, with metastatic disease being the most common cause. Other possibilities include an inflammatory process such as fungus, tuberculosis, nocardiosis, or septic emboli. In asymptomatic patients further considerations include the presence of arteriovenous malformations, rheumatoid nodules, or amyloidosis. Less common pulmonary lesions also include fibromas, chondromas, lipomas, hamartomas, and leiomyomas.

The radiological appearances as well as clinical features help to narrow the differential diagnosis down. On inspection of the radiograph one should note size, distribution, presence of cavitation, and that of calcification. Malignant tumours that commonly metastasise to the lungs include breast, thyroid, gastrointestinal tract and renal cell carcinomas, also head and neck tumours and soft tissue sarcomas. Metastases are present in variable numbers and are usually well defined and peripheral in distribution. Cavitation is occasionally seen with squamous cell carcinomas and calcification is unusual except for chondrosarcoma and osteosarcoma metastases. The main distinguishing features from benign lesions are the rate of growth and the presence of systemic symptoms. Hamartomas and carcinoid tumours have almost identical appearance on radiography, however most carcinoids are solitary with hamartomas being peripheral and often calcified and carcinoid being perihilar. Other conditions that cause multiple lung lesions are lymphoid malignancies and Kaposi's sarcoma. Finally infectious diseases including fungus granulomas, abscesses and hydatid disease and also connective tissue disorders should be considered. Fungus granulomas and hydatid disease may well be asymptomatic, while multiple abscesses will manifest with fever and symptoms proportional to their source. Rheumatoid nodules are usually small and rarely cavitate. Larger lesions are seen in Wegener's granulomatosis, but these are characteristically cavitating and often associated with haemoptysis and other symptoms of systemic vasculitis.

Q3: What important piece of information from the patient's past medical history is missing and would highlight a possible diagnosis?

The patient had had a total abdominal hysterectomy and bilateral salpingo-oophorectomy showing similar histology. She also had a right orchiectomy with a wedge resection for a 2 cm diameter encapsulated tumour at the age of 49 years. This condition is rather peculiar because of two contradictory findings: the tumour's benign histology and its metastasising capability. Unlike carcinoid tumours, malignant pulmonary metastases are uncommon.

Q4: What is the most likely diagnosis?

Spindle cell proliferation consistent with pulmonary leiomyomata secondary to a benign metastasising uterine leiomyoma.

References


A rare case of wheeze in a young adult

Q1: Describe the findings on radiography and computed tomography.

The plain radiograph and computed tomography of the chest (see p 543) demonstrated considerable reduction in the volume of her right lung with hyperinflation, a paucity of vascular markings on that side, and mediastinal shift to the right, suggesting a possible diagnosis of Swyer-James-MacLeod syndrome (a rare disease with unilateral hyperlucent lung due to bronchiolitis obliterans and pulmonary artery hypoplasia, which generally develops after lower respiratory tract infection during early childhood).

Q2: Describe the findings on bronchoscopy.

Bronchoscopy (see p 543) revealed a pigmented tumour causing almost complete obstruction of the right main stem bronchus at the level of the carina.

Q3: What is the most likely diagnosis?

An odd case of multiple “cannonball metastases”

The most likely diagnosis is a benign pigmented lung tumour, or a melanocytic carcinoma. The age of the patient, her general wellbeing and health apart from wheeze
on exertion, and never having smoked, make a malignant tumour unlikely.

Q4: How would you manage this patient?

Discussion

In our patient, a surgical opinion was sought, and a right upper lobectomy with sleeve resection of the right main stem bronchus and carina, with carinal reconstruction by tracheobronchial anastomosis was performed. Light microscopy disclosed a tumour composed of polygonal cells with clear and abundant intracytoplasmic glycogen, which was digested by diastase, indicative of glycogen granules. An extensive immunohistochemical panel was applied to the tumour, which revealed positivity to HMB-45 and S-100 protein.

The presence of prominent melanin pigment deposition and a very low mitotic index. Abdominal ultrasonography revealed no evidence of a primary intra-abdominal tumour. On review of three months later in the outpatient clinic, the patient was in excellent health, and pulmonary function tests had normalised, with an FEV1 of 2.29 L/min (95% of predicted value), and FVC of 2.68 L/min (91% of predicted value). The patient was now off all inhaled therapy, and her wheeze on exertion had resolved.

Benign clear cell tumour (BCCT) or “sugar tumour” of the lung is an unusual primary tumour originally described in 1963 by Liebow and Castleman. Since this time more than 40 cases of BCCT of the lung have been published worldwide, but there is only one prior report on the occurrence of a BCCT in the conducting airways.

Deep jaundice in an adolescent

Q1: What is the main differential diagnosis of this patient’s initial syndrome?

In this young girl a syndrome of fever, rash, transient hepatitis, and hepatic metastases ten years after resection of a benign tumour of the lung was reported by Liebow and Castleman. The differential diagnosis included a number of entities that were considered in this case, including Wilson’s disease, toxoplasmosis, and acute viral hepatitis.

Serological testing excluded acute viral hepatitis A, B, and C, which may be associated with icterus, low grade fever, lymphadenopathy, and hepatosplenomegaly. Autoimmune hepatitis may present with the same signs and symptoms, although acute icteric hepatitis as a presenting symptom is rather unusual.

The correct choice was to determine the cold agglutinin titre which was raised (1/1024) with an anti-“I” specificity. The glucose-6-phosphate dehydrogenase level was within normal limits and haemoglobin electrophoresis showed no abnormalities.

Box 1: Differential diagnosis of acute haematopoietic damage

- Viral hepatitis (hepatitis A, hepatitis B, Epstein-Barr virus, cytomegalovirus).
- Drug reaction (anabolic steroids, oestrogen).
- Granulomatous diseases (mycobacterial infections).
- Infiltrative malignancies (lymphoma).
- Inflammation of intrahepatic bile ducts (acute cholangitis, graft versus host disease, AIDS, cholangiopathy).
- Systemic bacterial infection.
- Alcoholic liver disease.

Box 2: Acute hepatocellular damage with prominent cholestasis

- Icteric viral hepatitis (hepatitis A, hepatitis B, Epstein-Barr virus, cytomegalovirus).
- Drug reaction (anabolic steroids, oestrogen).
- Granulomatous diseases (mycobacterial infections).
- Infiltrative malignancies (lymphoma).
- Inflammation of intrahepatic bile ducts (acute cholangitis, graft versus host disease, AIDS, cholangiopathy).
- Systemic bacterial infection.
- Alcoholic liver disease.

Box 3: Differential diagnosis of mononucleosis-like syndrome

- Epstein-Barr virus infection.
- Cytomegalovirus infection.
- Toxoplasma gondii infection.
- Streptococcal or gonococcal pharyngitis.
- Hepatitis virus A or B infection.
- Acute HIV infection.
- Hodgkin’s or non-Hodgkin’s lymphoma.
Q3: What is the diagnosis and the treatment of this syndrome?

Acute haemolysis due to cold agglutinins together with mononucleosis-like syndrome and icteric hepatitis suggests an acute and severe Epstein-Barr virus infection. The IgM antibodies against Epstein-Barr virus capsid antigen were raised in a titre of 1/320 and the IgG antibodies 1/160. Whole blood examination with polymerase chain reaction for Epstein-Barr virus DNA was positive.

In patients with Epstein-Barr virus hepatitis and/or cholestasis, conservative measures are usually sufficient. In patients in whom haemolysis due to cold agglutinins occurs, corticosteroid therapy is controversial but sometimes recommended, although it is of proven benefit in the case of autoimmune haemolysis due to warm antibodies.

Progress

The patient started folate administration and a short course of corticosteroid treatment. Her condition progressively improved. Packed cell volume, bilirubin, and cold agglutinin titres during follow up are shown in fig 1. She was discharged on the 20th postadmission day with a packed cell volume of 32%, haemoglobin 106 g/l, reticulocyte count 3.9%, total bilirubin 3.8 mg/dl (65 µmol/l), direct bilirubin 3.04 mg/dl (52 µmol/l), and still moderately raised liver enzymes. Six months later the patient was in good health with complete clinical and biochemical recovery.

Discussion

This young patient presented with a severe Epstein-Barr virus infection complicated by icteric hepatitis and secondary haemolysis due to cold haemagglutinins. Nevertheless, lack of the classical symptoms of infectious mononucleosis and the negative test for heterophil antibodies made the initial diagnosis difficult. The rapid heterophil antibody test has an important role in the diagnosis of Epstein-Barr virus infection. However, false negative tests have been reported in 20% of the cases in children and 15% in adults.

At presentation, a moderate hepatocellular injury, with raised liver enzymes, a normal prothrombin time but unusual high conjugated bilirubin level was predominant. Any other causes of acute hepatocellular damage and intrahepatic cholestasis have been excluded. Acute hepatitis at presentation is reported in 20%–30% of the cases of Epstein-Barr virus infection, however, mild hyperbilirubinaemia is present in only half of these patients. Cases of cholestasis with clinical relevant deep jaundice are rarely reported, with peak serum bilirubin levels ranging from 18 mg/dl (308 µmol/l) to 23 mg/dl (393 µmol/l).

During hospitalisation our patient presented a rapid fall in haemoglobin level (from 116 g/l to 65 g/l) and her jaundice became “deeper”. The initial high bilirubin levels resembling predominantly conjugated bilirubin (68% of the total bilirubin level) became more raised with a switch to predominantly unconjugated bilirubin (62.5% of the total bilirubin level). The finding of high anti-“i” cold agglutinins titre demonstrated that acute haemolysis had complicated the course of the disease. Anti-“i” cold agglutinins may be present in fewer than 2% of patients with Epstein-Barr virus infection but clinically relevant haemolytic anaemia is usually mild and self limiting.

Severe haemolysis with an important fall in haemoglobin level and deep jaundice, as in our patient, has rarely been described. In a previous study, seven patients with primary Epstein-Barr virus infection had peak bilirubin levels of 10.2–23 mg/dl (174–393 µmol/l). In five of these seven cases, however, there was evidence for both hepatocellular dysfunction and an ongoing haemolytic process either due to anti-“i” cold agglutinins or due to positive anterythrocyte antibodies.

Deep jaundice with signs of haemolysis always raises the possibility of Wilson’s disease. In our patient serum ceruloplasmin and copper were normal and no increased urinary copper or the presence of Kayser-Fleischer ring could be documented. Although these findings do not absolutely exclude Wilson’s disease, the fact that the patient is healthy now, more than six months after the episode of jaundice, clearly demonstrates that she can not have any chronic metabolic disease.

In conclusion, classical Epstein-Barr virus infection is usually a benign and self limiting disease. Despite this fact, close follow up of cases in order to prevent and identify possible complications is necessary. The present case should raise clinicians’ indices of suspicion for the described unusual complications of the well-known syndrome of infectious mononucleosis. A cholestatic form of Epstein-Barr virus induced hepatitis may be present in several cases, while a deepening jaundice may be the result of haemolysis due to cold haemagglutinins.

Final diagnosis

Epstein-Barr virus infection.

References

A diagnostic conundrum

Postgrad Med J 2003 79: 545-546
doi: 10.1136/pmj.79.935.545-a

Updated information and services can be found at:
http://pmj.bmj.com/content/79/935/545.2

These include:

References
This article cites 4 articles, 1 of which you can access for free at:
http://pmj.bmj.com/content/79/935/545.2#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/