Generalised oedema, lethargy, personality disturbance, and recurring nightmares in a young girl

Q1: What is the likely diagnosis?
The low serum copper and caeruloplasmin concentrations, in the setting of abnormal liver function, hyponatraemia, and profound clotting disturbance point to a diagnosis of Wilson’s disease with hepatic failure. In this case, hepatic involvement predominates despite background lethargy, personality change, and depression. The prominent abdominal veins, fluid retention, and ascites are the clinical manifestations of portal hypertension and decompensated liver disease, with poor synthetic function evidenced by a low serum albumin and greatly increased prothrombin time.

Her shortness of breath was secondary to abdominal distention and diaphragmatic splinting due to ascites. A polyclonal immunoglobulin rise is often seen in Wilson’s disease and a raised serum B12, which is stored in the liver, is associated with hepatic necrosis.

Q2: What further investigations would confirm the diagnosis?
Classically, serum caeruloplasmin concentrations are very low in parallel with low serum copper levels. Though serum caeruloplasmin estimation alone is not specific enough to diagnose Wilson’s disease, concentrations as low as in this case are unusual for any other diagnosis. Caeruloplasmin synthesis can be modestly reduced in decompensated liver disease of any aetiology or in acute liver failure. Protein losing enteropathy, nephrotic syndrome, and malnutrition will also reduce serum concentrations. Conversely, as its synthesis can be stimulated by oestrogens and it is an acute phase reactant, its concentrations can be calculated—though high values (>200 µg/l) suggest Wilson’s disease, diagnosis based on such calculation lacks specificity and is dependent on the accuracy of copper and caeruloplasmin measurement.

A 24 hour copper estimation is a simple and useful confirmatory test with raised values (>100 µg/24 hours) invariably seen in symptomatic Wilson’s disease. Concentrations in this case were greatly raised at 461 µg/24 hours (normal range 0–50). Care needs to be taken to ensure the collection is accurate and has not been contaminated (for example extraneous copper in tap water). Verification of the result by a repeat collection is advisable. Borderline values may be obtained in presymptomatic patients or heterozygotes, such results demand further investigation.

A liver biopsy, in itself, may not be diagnostic but is helpful in determining the extent of hepatic involvement and whether or not there is established cirrhosis. In this case, given the background coagulopathy, a transjugular liver biopsy was performed which confirmed established cirrhosis. Fibrosis and moderate inflammatory change was accompanied by extensive collapse of residual liver between regenerative nodules suggesting recent subacute necrosis. A mild increase in copper associated protein and copper accumulation in the hepatocellular nodules was felt to be consistent with Wilson’s disease. Occasionally, despite gross hepatic copper excess, histochemical techniques may fail to demonstrate copper. Determination of hepatic tissue copper concentration by neutron activation analysis or atomic absorption spectrometry may clearly indicate hepatic copper overload. Concentrations greater than 250 µg/g dry weight are accepted as diagnostic of Wilson’s disease.

Slit lamp examination to look for KF rings may also be helpful, although these are absent in 15%–50% of patients with an exclusively hepatic presentation. It should also be recognised that though KF rings are generally specific for Wilson’s disease in children, this is not the case in older patients, where they may be associated with other types of chronic liver disease (usually with a cholestatic component) and non-hepatic diseases. In this case, because of the liver biopsy findings, copper result, and deteriorating clinical condition no slit lamp examination was performed.

Q3: What treatment options might you consider and how would you manage this young girl?
The two main treatment options are chelation treatment with penicillamine or referral to a liver unit for consideration for orthotopic liver transplant (OLT). Chelation therapy is the treatment of choice in patients with compensated liver disease. A satisfactory response, even in the setting of decompensated cirrhosis, ascites, and coagulopathy has been described, as long as encephalopathy has not developed, though early referral to a liver unit is preferable in the setting of deteriorating liver function as OLT is curative.

The usual starting dose is 250 mg daily increasing over a period of a few weeks to an eventual maintenance dose of 1.5 g daily. Approximately 20% of patients will experience side effects such as fever, rash, leucopenia, thrombocytopenia, and lymphadenopathy. An systemic lupus erythematosus-like syndrome and proteinuria may also occur. Trientine is an alternative chelating agent which may be used in those unable to take penicillamine. Elemental zinc inhibits gastrointestinal copper absorption but its long term effectiveness is unproven.

Success of therapy is judged by clinical improvement. This may be slow and 25% of patients with neurological presentations may
initially deteriorate. The dose of penicillamine can be increased further if, despite adequate compliance, there has been no initial response. Liver function should improve and hepatic biopsy shows lessening of activity and reversion to inactive cirrhosis. KF rings fade and eventually disappear, mental performance improves, and neurological signs such as tremor and rigidity, lessen. Improvement in handwriting is a good test of progress. Given such improvement, the dose of penicillamine is reduced to a maintenance dose of 750–1000 mg daily. After two years, failure to respond implies the presence of irreparable tissue damage or poor compliance. A fulminant course may follow non-compliance in a previously well controlled patient.

In patients with decompensated liver disease unresponsive to medical therapy or presenting with fulminant hepatic failure, OLT is the treatment of choice. Given the extensive subacute necrosis on the liver biopsy, poor hepatic synthetic function and signs of liver decompensation our patient underwent urgent OLT, made an eventful recovery and was discharged home on standard immunosuppression. She has had three normal pregnancies and remains well six years after her transplant.

**Discussion**

Kinnear Wilson, in 1912, first used the term “progressive hepatolenticular degeneration” to describe a familial disorder with neurological disease, chronic liver disease, and KF rings. Wilson’s disease is an autosomal recessive condition. The WND gene, which encodes a membrane P-type ATPase transporter, is located on chromosome 13. Several specific mutations have been identified, the commonest in European populations being the H1069Q mutation with a frequency of between 26%–70%. The reported incidence is 1:30,000 giving a carrier frequency of approximately one in 90.

The functional disruption to the membrane transporter affects incorporation of copper into caeruloplasmin (a 132 Kda ß-glycoprotein) and its excretion into bile. Positive copper balance results with accumulation of unbound copper in the liver. An array of extrahepatic disorders associated with Wilson’s disease demonstrate the wider organ involvement. In addition to the well described KF ring (accumulation of copper in Descemet’s membrane of the posterior cornea), renal tubular disease (leading to secondary renal stones, osteoporosis, or osteomalacia), arthritis, pancreatitis, cardiomyopathy, rhabdomyolysis, and a variety of endocrine disorders have been ascribed to end organ copper deposition.

Liver damage is evident early in the natural history. Hepatocytes are ballooned, show multiple nuclei, clumped glycogen, and glycogen vacuolation. Fatty change is usual. Kupffer cells are large, with stained copper tending to be within these, rather than hepatocytes. Mallory’s bodies may be seen, simulating acute alcoholic hepatitis. All grades of change from periportal fibrosis, through submassive necrosis, to a coarse micronodular cirrhosis are seen. Cell injury is thought to result from oxidant damage. The wide variation in host response and clinical heterogeneity probably results from genetic and environmental influences on copper protective mechanisms. Knowledge of the specific genetic mutation does not allow precise prediction of subsequent clinical outcome.

Patients may be symptomatic or diagnosed after investigation of incidental liver function abnormality. Presenting features are either hepatic, neurological (movement disorders or rigid dystonia patterns), or psychiatric (depression, neuroses, personality changes). A degree of overlap is recognised, as illustrated by this case, where the predominant hepatic presentation was associated with personality change and depression. Such personality changes may be difficult to distinguish from the clinical syndrome of encephalopathy. In general, patients with the hepatic form are younger (less than 19 years), whereas patients presenting after the age of 20 frequently have neurological or psychiatric symptoms.

The pattern of hepatic presentation of Wilson’s disease can be divided into fulminant hepatitis, chronic hepatitis, or cirrhosis. The fulminant type is characterised by progressive jaundice, hypoalbuminaemia, ascites, coagulopathy, encephalopathy, and renal failure. Virtually all patients are already cirrhotic. Hepatic necrosis may lead to a sudden flux of copper...
into the vascular compartment resulting in acute haemolysis, haemolytic anaemia, and raised serum bilirubin concentrations. The alkaline phosphatase/bilirubin ratio is usually low, unlike fulminant viral hepatitis. Chronic hepatitis usually presents between 10–30 years, with jaundice, high transaminases, and hyper-gammaglobulinaemia. Cirrhotic patients may present insidiously with signs of chronic liver disease and portal hypertension. Hepatocellular carcinoma complicating cirrhosis in Wilson’s disease is rare.

Untreated Wilson’s disease is progressive. Response to chelation therapy may be poor in patients with chronic hepatitis and the fulminant form is frequently fatal. Liver transplantation is potentially lifesaving and corrects the underlying metabolic abnormality. It is therefore vital to consider the diagnosis in a young person presenting with liver function abnormalities. Survival in patients transplanted for Wilson’s disease was 79% at one year in one series. At Queen Elizabeth Hospital, Birmingham, between 1982 and 1995, 15 out of 1181 (1.3%) of transplants were for Wilson’s disease, eight for fulminant presentations (mean age 15 years; range 7–24), and seven for chronic liver disease (mean age 20 years; range 11–48). Two patients in the fulminant group died in the immediate post-OLT period, however all patients with chronic presentations survived transplant and remain well.

Screening of siblings after appropriate genetic counselling is mandatory, each having a one in four chance of being affected. Figure 1 shows the patient’s family pedigree. Traditional screening involving physical examination, liver function tests, serum copper and caeruloplasmin measurement, basal 24 hour urinary copper estimation, and a careful slit lamp examination is now used alongside genetic testing. The typing of flanking microsatellite markers is now available routinely in most diagnostic laboratories. Where the index case has been identified this provides the most reliable method of determining the genetic status of the siblings or other relatives. However, such screening is not necessary for children of those affected, unless their partner is known to be a gene carrier, due to the autosomal recessive nature of the disease and sufficiently low gene carrier rate. No known heterozygote has been reported to have developed disease symptoms. Therefore initiation of presymptomatic treatment should be reserved for those homozygous for the Wilson’s gene.

Final diagnosis
Wilson’s disease with hepatic failure.

An unusual pituitary mass presenting with panhypopituitarism and hyponatraemia

Q1: What is the differential diagnosis of an intrasellar mass?
For the differential diagnosis see box 1.

Pituitary adenoma accounts for >85% of the cases of intrasellar masses, all other causes contribute to <15% in the adult population. Schwannomas and germ cell neoplasms are rare occurrences in the intrasellar region.

Q2: What is the cause of the intrasellar mass in this patient and what are its diagnostic features?
This patient’s intrasellar mass was due to a schwannoma. The histopathological features of schwannomas are:
- Fascicular arrangement of spindle shaped cells with cigar and cigarette shaped nuclei.
- The positivity of tumour cells with S-100 stain and EMA negativity.
- Electron microscopic evidence of basal laminae.

Q3: What is the cause of hyponatraemia in this patient?
Dilutional hyponatraemia was caused by glucocorticoid deficiency.

Discussion
Schwannomas constitute about 8% of all primary intracranial tumours. The most common site is the acoustic nerve. Other cranial nerves which have been reported to be the sites of occurrence of schwannomas are the trigeminal, facial, and the hypoglossal nerves. A schwannoma presenting as an intrasellar mass is a rare occurrence. Previously, five cases of intrasellar schwannomas have been reported in the literature. The rare occurrence of

### Box 1: Differential diagnosis of an intrasellar mass

1. Neoplasms
   - Pituitary adenoma (>85% of all cases).
   - Craniopharyngioma.
   - Meningioma.
   - Germ cell neoplasm (rare).
   - Chordoma.
   - Granular cell tumour.
   - Schwannoma (rare).
   - Metastases.

2. Cysts, hamartomas, and malformations
   - Rathke’s cleft cyst.
   - Epidermoid/dermoid cyst.
   - Arachnoid cyst.
   - Hypothalamic hamartoma.

3. Inflammation
   - Lymphocytic hypophysitis.
   - Sarcoidosis.
   - Langerhans’ histiocytosis.
   - Giant cell granuloma.

4. Vascular
   - Aneurysms.
   - Cavernous angioma.


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schwannomas in the sella turcica is due to the absence of schwann cells in the sella. The only nerve fibres in the intrasellar region are the neurosecretory fibres of the posterior pituitary. However, these nerve fibres lack schwann cells as these are direct extensions of the hypothalamic and central nervous system neurones. Various hypotheses are postulated to explain intrasellar schwannomas. First, perivascular schwann cells could be the origin of these tumours. Second, the origin of intrasellar schwannomas could be the schwann cells of small fibres innervating the dura. Dural attachment of the tumour as reported by Civit et al and Guenot et al supports this hypothesis. However, in our patient, the tumour was not adherent to the dura. Our patient presented with panhypopituitarism, as did the patients reported by Guenot et al and Wilberger. However, the patients reported by Civit et al and Perone et al had intact neuroendocrine function. The patient reported by Goebel et al presented with loss of consciousness and involuntary movements. These authors did not mention the neuroendocrine status of the patient.

Another interesting aspect of our case was the association of hyponatraemia. Hyponatraemia in association with pituitary insufficiency has been described earlier. Hyponatraemia is noted in patients with primary as well as secondary adrenal insufficiency. Glucocorticoids are postulated to exert an inhibitory effect on the secretion of antidiuretic hormone (ADH). Thus, deficiency of glucocorticoids could lead to the syndrome of inappropriate ADH secretion (SIADH) and dilutional hyponatraemia. Oelkers has reported five patients with hyponatraemia and panhypopituitarism who had inappropriately high concentrations of ADH. After glucocorticoid replacement, the serum sodium concentration normalised with normalisation of plasma ADH and osmolality. Glucocorticoids have also been shown to increase the free water clearance by the renal tubules. Lack of glucocorticoids can decrease free water clearance and contribute to low serum sodium concentrations. Gonzales-Portillo and Tomita have reported three cases of childhood craniopharyngioma with SIADH, and have postulated a direct mechanical stimulation of the hypothalamic nuclei leading to inappropriate ADH secretion.

Our case, in the context of the other reported cases of an intrasellar schwanna, points out the rarity of such an occurrence and illustrates the spectrum of neuroendocrine abnormalities, from none to panhypopituitarism, which can be seen in such individuals.

**Final diagnosis**

Intrasellar schwannoma.

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**Box 2: Key points**

- Even though rare, schwannomas can present as an intrasellar mass.
- The pathological features of schwannomas are: fascicular arrangement of spindle shaped cells with cigar and cigarette shaped nuclei; tumour cells positive for S-100 stain and negative for EMA; basal laminae evident on electron microscopy.
- Glucocorticoid deficiency can cause dilutional hyponatraemia by: loss of inhibitory effect on ADH secretion; decreased free water clearance by renal tubules.

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restrictive picture. This could occur for instance with lymph node obstruction of a large airway as well as parenchymal disease.

Discussion

Neurological presentation occurs in approximately 5% to 16% of patients with sarcoidosis. 1 2 Seventh nerve involvement is the most common presenting neurological feature and mononeuritis multiplex as illustrated by this case is not uncommon. Sarcoidosis presenting with pancreatitis, however, is rare. Hilar lymphadenopathy is the most common abnormality on chest radiography in sarcoidosis. In some cases, however, this may only be obvious on computed tomography of the chest. 2 3

High resolution computed tomograms are useful in the evaluation of diffuse infiltrative lung disease in which case they have been shown to be superior to conventional radiography. 2

Hypercalcaemia is another feature and is due to the 1α-hydroxylation of vitamin D, that occurs within the macrophages of the granulomas. It occurs in about 10% of patients. 4 A raised ACE level occurs in almost two thirds of patients. Its place in diagnosis is debatable, as raised levels may occur in many other diseases including asbestososis, silicosis, berylliosis, fungal infection, granulomatous hepatitis, hyper-sensitivity pneumonitis, leprosy, lymphoma, and tuberculosis. However serial measurements are useful for monitoring disease activity and response to treatment. Liver involvement with microscopic, non-caseating granulomas is common and biopsy will reveal granuloma in almost 90% of cases. However, studies have shown white people to have a lower yield of granulomas on biopsy and this should be borne in mind by attending physicians. 5

Sarcoidosis is a multisystemic illness and may affect any part of the body. Stage I pulmonary disease, that is hilar and mediastinal lymph node enlargement alone, usually remits spontaneously and has not been shown to benefit from steroid therapy. Early treatment with systemic corticosteroid (for example prednisolone 1 mg/kg/day initially) is warranted in extrapulmonary disease, such as in our case where there was a danger of irreversible neurological and ocular damage. Treatment once started is continued for several months and tailed down once markers of disease activity improve. Other agents that have successfully been tried in the long term management of refractory neurosarcoidosis include methotrexate and cyclophosphamide. 3

Outcome

A diagnosis of neurosarcoidosis with pancreatic and liver involvement was made and our patient was started on prednisolone 60 mg daily. She made remarkably good progress and was well enough to be discharged two weeks later. At follow up after four weeks, there had been complete resolution of the facial nerve weakness and the only residual neurology was mild paraesthesia over the left knee.

Final diagnosis

Neurosarcoidosis with pancreatic and liver involvement.

Q1: What are the differential diagnoses?

The most important differential diagnosis to consider in a young patient with multiple colorectal polyps is that of familial adenomatous polyposis. Other conditions that might be considered are hyperplastic polyposis coli, Peutz-Jeghers syndrome, multiple juvenile polyposis, Gardener’s syndrome, Cronkhite-Canada syndrome, Turcot’s syndrome, Cowden’s syndrome, and pseudopolypsis secondary to ulcerative colitis.

Q2: What is the diagnosis for these patients?

Hyperplastic polyposis coli.

Q3: How would you manage patients with this diagnosis?

Regular colonoscopy with polypectomy may be sufficient. Prophylactic colectomy, as would be advocated in familial adenomatous polyposis, is probably not warranted in this condition unless a secondary carcinoma is detected.

Discussion

Hyperplastic polyps of the colon are common benign lesions. They frequently arise at the crest of a mucosal fold where they present as small, sessile polyps usually measuring less than 5 mm in diameter with a smooth convex surface. 6 Although traditionally regarded as non-neoplastic, recent evidence has shown hyperplastic polyps to have molecular features of neoplasia. 7

Histologically they have a very characteristic appearance of elongated crypts with prominent epithelial infoldings giving a pathognomonic serrated pattern. The majority of hyperplastic polyps occur in the rectosigmoid where they may be single or often multiple; however their numbers rarely exceed 10 . 7 The occurrence of multiple or large hyperplastic polyps in the large bowel is termed hyperplastic polyposis coli. 7 3 4

Hyperplastic polyposis coli is a rare condition characterised by the presence of large multiple hyperplastic polyps, some of which may show dysplasia, an occurrence that is felt to contribute significantly to the observation that approximately 40% of sporadic cases are associated with adenocarcinoma. 1 Hyperplastic polyposis coli has recently been more clearly defined by

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Jørgensen et al as “at least 20 polyps distributed evenly or segmentally in the colorectum or at least two polyps larger than 10 mm in diameter”. Place et al have advanced a different definition of what they call hyperplastic adenomatous polyposis syndrome. They define this as at least 50 polyps, including adenomatous polyps, greater than 5 mm in diameter and associated with adenocarcinoma of the colon. Unfortunately this definition excludes the majority of cases reported in the literature as hyperplastic polyposis syndrome. One family has also been reported with eight affected individuals in three generations, six of whom had adenocarcinoma. Only one of these eight cases fulfilled the criteria advanced by Jørgensen et al.

The dysplasia seen in these polyps (see fig 1) is that of a mixed hyperplastic-adenomatous polyp showing areas of unequivocal benign hyperplastic morphology and areas of unequivocal dysplastic adenomatous morphology within the same polyp. This pattern is different from serrated adenoma where the entire polyp shows dysplasia within a polyp showing a serrated growth pattern. Hyperplastic polyposis coli should be distinguished from adenomatous polyposis coli as suggested by Törkovic et al.

Confusion in an elderly patient: an uncommon diagnosis for such a common event

Q1: What is the initial diagnosis?
For an elderly patient developing cognitive impairment with insomnia, agitation, and functional decline over a short period of time, the most probable diagnosis is acute delirium. Without clues to the diagnosis after basic evaluation, the question to be asked in such a case is: is this drug related? Either due to a newly introduced drug or a drug withdrawal. In this case, careful discussion with the family revealed that the patient’s cognitive decline began after a recent medical check-up.

Q2: In view of the results, which diagnosis should be considered and which parameters shall be measured?
In this case, the prescription of levothyroxine therapy should be involved because cognitive impairment coincided with the beginning of the treatment. The possibility of iatrogenic hyperthyroidism should be considered. It must be stressed that an increase in TSH is not specific enough for the diagnosis of hyperthyroidism, and that confirmation of low thyroid hormone levels is needed. Indeed, this patient’s medical record showed that the increased TSH was associated with a high normal free thyroxine (21.9 pmol/l; normal values 0.7–1.8) before any treatment. Hormone values at hospital admission revealed frank hypothyroxinaemia (free thyroxine 3.3 pmol/l) and confirmed the persistence of an increased TSH level (5 mIU/l). Thyroxine therapy was therefore stopped and the cognitive symptoms completely disappeared in a few days. The association of increased TSH, not suppressed by thyroxine therapy, and a pituitary macroadenoma led to the diagnosis of TSH secreting pituitary adenoma. Considering the age and frailty of the patient, it was decided in agreement with the family doctor and the relatives to avoid pituitary surgery. An asymptomatic corticotropic deficit was diagnosed and replacement therapy started. The patient was doing well at outpatient follow up with a TSH of 5.3 mIU/l at six months.
Self assessment answers

Learning points
- Classical symptoms of hyperthyroidism are of poor diagnostic use in the elderly.
- Acute cognitive impairment is frequently related to drug modification.
- Occasionally, raised TSH is not caused by hyperthyroidism.

Discussion
Thyrotrophic adenomas are very rare, or at least rarely diagnosed. To date about 300 cases have been described in the literature, with the largest series including 25 cases recently published by the National Institutes of Health. This is a very unusual diagnosis, and it is important that endocrine data should be correctly interpreted when diagnosing hyperthyroidism in elderly people.

The difficulty in diagnosing hyperthyroidism is often underestimated, not only in elderly people but also in people receiving common drugs inducing the signs of hypothyroidism (β blockers and sedatives) or inhibiting TSH values (corticosteroids). The formal diagnosis of hyperthyroidism may be very elusive. A high degree of suspicion is mandatory when facing suggestive symptoms such as mood disorder, restlessness, wasting, insomnia, heart failure, and/or delirium in elderly people, as in our case. Tachycardia is often absent, and tremor is so common in elderly people that it is not taken into account. Another much less common diagnostic pitfall is illustrated by our case: raised TSH associated with hyperthyroidism. Only four circumstances account for this rare event: laboratory error, pituitary thyrotrophic adenoma, peripheral resistance to thyroid hormones and, more commonly, the recent introduction, or poor compliance, with intermittent use of liberal levothyroxine substitution in hypothyroid patients. Thus, special attention should be paid to the evaluation of thyroid tests in elderly people in which high TSH is not always a proof of hyperthyroidism, as clearly demonstrated in this case of iatrogenic hyperthyroidism inducing delirium.

Final diagnosis
Iatrogenic hyperthyroidism with delirium and TSH secreting pituitary macroadenoma.

Siblings with multiple soft tissue calcifications
Q1: What are the radiological findings?
The radiograph of the left knee of the younger brother (fig 1; p 534) shows calcification in the periarticular soft tissues. Radiographs of both the elbows and forearms (figs 2 and 3; p 534) of the elder brother show calcification in the periarticular soft tissues and muscles.

Q2: What is the diagnosis?
The diagnosis is tumoral calcinosis (normophosphataemic type). The differential diagnosis includes other conditions causing soft tissue calcification—that is, myositis ossificans, calcified fracture haematoma, and systemic lupus erythematosus with secondary calcinosis.

Q3: What is the pathogenesis and treatment of this condition?
The pathogenesis of tumoral calcinosis is not yet clearly established. It is said to occur as a result of deranged calcium-phosphorus metabolism. It can also occur as secondary to systemic disorders like chronic renal failure, hyperparathyroidism, and systemic lupus erythematosus. All these conditions also cause deranged calcium-phosphorus metabolism.

The treatment includes phosphate depletion in the diet (in hyperphosphataemic variant), topical steroid application, surgical excision of calcified deposits causing pain or limitation of joint movements, and curettage of sinuses discharging calcareous material.

Discussion
Tumoral calcinosis is a genetic, metabolic disorder, characterised by deposition of calcium salts in the subcutaneous tissues of the body. The condition is inherited as an autosomal recessive trait. Common sites affected are hip, shoulder, elbow, and ankle joints with the hip joint being the site most commonly affected. Curiously the knees are usually spared. One of the boys described here had an involvement of the knee joint, which is rare.

The condition is said to occur as a result of deranged calcium-phosphorus metabolism with consequent hyperphosphataemia. Cases with normal serum phosphorus concentrations have also been reported and recently a pathological classification based on serum phosphorus concentrations has been suggested. Thus, patients can be classified as hyperphosphataemic or normophosphataemic.

Learning points
- Tumoral calcinosis is a genetic disorder of calcium-phosphorus metabolism.
- It is inherited as an autosomal recessive trait.
- The condition occurs secondarily in systemic disorders like chronic renal failure, systemic lupus erythematosus, and hyperparathyroidism.
- The hip is the commonest site of involvement.

In addition to subcutaneous calcium salt deposition, ophthalmic examination can reveal subretinal angioid streaks and dental radiograms may show pathognomonic short, bulbous roots and partial obliteration of pulp cavities. These features were not seen in our cases. The calcification pattern in tumoral calcinosis is very characteristic with large, juxta-articular lesions, progressive enlargement over time, and a tendency to recur after surgical removal.

**Final diagnosis**
Primary normophosphataemic tumoral calcinosis.

2 Pakasa NM, Kalengayi RM. Tumoral calcinosis; a clinicopathological study of 111 cases with emphasis on the earliest changes. *Histopathology* 1997;31:18–24.

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**Questions**

**Q1:** At presentation what diagnosis would you consider in this patient and how does this relate to the findings on examination of the cardiovascular system?
Severe abdominal pain with bloody diarrhoea raises the possibility of ischaemic colitis. Initially the symptoms are often disproportionately more severe than the findings on examination. The presence of a marked leucocytosis or metabolic acidosis often reflects the presence of necrotic bowel. In addition, a raised serum amylase may be found in the presence of small bowel infarction. In this patient, at laparotomy all bowel supplied by the superior mesenteric artery was necrotic, nonviable, and hence required resection. This patient was noted to have splinter haemorrhages, to be in atrial fibrillation, and to have a diastolic murmur. Subsequent investigations demonstrated an atrial myxoma as the cardiac source for the embolus that had occluded the superior mesenteric artery.

**Q2:** How are feeding and fluid requirements assessed in patients who have undergone intestinal resections and what plans should be made for nutritional support for this patient after laparotomy?
Patients with at least 80–100 cm of small bowel, particularly when the colon remains, can often manage to maintain nutrition with enteral support. However with only 20 cm of remaining small bowel this patient will require life long parenteral nutrition. A dedicated, single lumen, central line was inserted at the time of operation and parenteral nutrition feeding started immediately.

**Q3:** What has happened to the patient three months after surgery and what caused the carpopedal spasm?
Patients with short bowel experience problems with fluid loss and electrolyte imbalance due to severe diarrhoea. This patient developed acute renal failure as a result and required dialysis for one month in addition to intravenous correction of the hypovolaemia. Partial recovery of renal function occurred to a serum creatinine of 250 µmol/l. Patients with short bowel can also lose magnesium from the gastrointestinal tract. On admission, the patient was mildly acidoletic and the serum magnesium concentration was 0.42 mmol/l, which was the cause of the carpopedal spasms. Serum calcium concentration was within the normal range. Correction was initially with intravenous magnesium and subsequently with life long oral supplementation. Magnesium oxide tends not to exacerbate diarrhoea in short bowel. In addition 1-α cholecalciferol, correcting secondary hyperaldosteronism (see discussion), and reducing lipid in diet are treatments for hypomagnesaemia. One possible cause of acidosis is D-lactic acidosis. This is caused by abnormal colonic bacterial production of the D isomer of lactic acid, which cannot be metabolised, in patients on a high carbohydrate diet. It is more common with coexistent thiamine deficiency and presents with ataxia, ophthalmoplegia, and nystagmus. Treatment is with antibiotics and a low oligosaccharide diet.

**Discussion**
Short bowel usually occurs after extensive resection of the small bowel. The commonest causes are Crohn’s disease and vascular occlusion (arterial embolus, mesenteric vasculitis, or venous thrombosis). The need for parenteral nutrition after surgery depends on the length of remaining small bowel and whether a colon remains. If a colon remains, those patients with less than 50 cm of residual small bowel are likely to require long term parenteral nutrition. If a jejunostomy is present, those patients with less than 100 cm of small bowel can be expected to require parenteral nutrition. Nutritional status can be assessed and monitored by measures such as body mass index (weight (kg)/height (m)²; normal range 20–25 kg/m²) and mid-arm circumference. In addition, to malnutrition, patients experience fluid and electrolyte loss and may require parenteral supplementation. The diarrhoea can be reduced by the use of proton pump inhibitors which reduce gastric secretions, a low fat diet (in those patients with a colon), and motility reducing agent such as loperamide at higher than usual doses. Sodium loss from the gastrointestinal tract can be compensated for by drinking fluid with added salt (equivalent to World Health Organisation oral rehydration solution or approximately double concentrated Dioralyte), although when a colon remains the need for this is small. The hyponatraemia on admission in this patient reflected marked volume depletion due to gastrointestinal fluid loss. Hyponatraemia of this type is largely due to hypovolaemia stimulated antidiuretic hormone...
secretion rather than simple sodium depletion. Urinary sodium concentration is also a reflection of plasma volume, because it is determined by the activity of the renin-angiotensin-aldosterone system. A low urinary sodium concentration (<10 mmol/l) in patients with short bowel reflects ongoing hyperaldosteronism secondary to volume depletion and indicates the need for additional fluid supplementation. In addition to hypovolaemia due to fluid loss, other causes of renal failure such as obstructive nephropathy should be considered. Calcium oxalate renal stones can occur in patients with a retained colon due to increased colonic absorption of oxalate following ileal resection. Hypomagnesaemia, due to increased gastrointestinal loss is a common consequence of short bowel. The neuromuscular manifestations such as the carpopedal spasm usually occur in the presence of an acidosis as in this case. In addition, hypomagnesaemia can exacerbate other electrolyte disturbances such as hypokalaemia, hypocalcaemia, and hypophosphataemia. Serum magnesium concentration should be monitored in all patients with significant gastrointestinal disturbance. Parenteral nutrition for those patients, who require it, should be given via a dedicated single lumen central line. This has been shown to reduce the incidence of complications such as catheter related infections. Patients can be taught to care for central lines and manage their parenteral nutrition feeding at home. Many such patients, with appropriate support, undertake long term feeding for many years without complications or the need for line changes. The care of parenteral nutrition patients at home requires a multidisciplinary approach involving gastroenterologists, specialist nutrition nurses, biochemists, dietitians, and pharmacists. Further guidance on the management of patients with a short bowel can be obtained by reading a detailed review article.1

Heart failure, a thick tongue, and an abnormal cranial computed tomogram

Q1: What is the underlying condition, which can explain his thick tongue and cranial computed tomogram abnormalities?

Chronic hypocalcaemia can explain his symptom and sign of a thick tongue, and cranial computed tomography finding of bilateral basal ganglia calcification. His thick tongue was a manifestation of Schultz's sign of latent tetany: a mechanical stimulation of the tongue is followed by local muscle contraction.2

Clinically Chvostek's and Trousseau's signs were positive. The electrocardiogram revealed sinus tachycardia, and a corrected QT interval of 0.56 seconds (normal 0.36–0.43). Serum calcium was 1.03 mmol/l (2.12–2.62), phosphorus 3.48 mmol/l (0.8–1.4), vitamin D3 concentration 23 pmol/l (36–144), and serum parathyroid hormone concentration 1.2 pmol/l (10–65). The blood counts and concentrations of serum sodium, potassium, magnesium, and creatinine were normal. The serum alkaline phosphatase was 168 U/l (40–125), lactate dehydrogenase 2860 U/l (230–460), and creatine phosphokinase 674 U/l (30–200). The low parathyroid hormone with severe hypocalcaemia indicated hypoparathyroidism, most probably idiopathic hypoparathyroidism.

Q2: What is the pathophysiology of his cardiac failure?

The pathophysiology of his cardiac failure is chronic hypocalcaemia leading to hypocalcaemic dilated cardiomyopathy and cardiac failure. Hypocalcaemia leads to decreased myocardial contractility, clinically this may translate into congestive heart failure. The congestive cardiac failure in hypocalcaemia is refractory to diuretics and digitalis but rapidly responds to restoration of calcium concentrations to normal.3 Calcium infusion increases both cardiac output and blood pressure in hypoparathyroid patients suggesting a subclinical direct cardiac dysfunction due to hypocalcaemia,4 but hypomagnesaemia and reduced circulating parathyroid hormone may also be involved in causing dilated cardiomyopathy in hypoparathyroidism.5

Q3: What are the other cardiovascular manifestations of this condition?

For other cardiovascular manifestations of this condition see box 1.

Follow up

Echocardiography showed enlarged left and right ventricles, and mitral and tricuspid regurgitation. Hypocalcaemic cardiomyopathy with

<table>
<thead>
<tr>
<th>Box 1: Other cardiovascular manifestations of hypocalcaemia</th>
</tr>
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<tbody>
<tr>
<td>• Prolongation of QT interval.6</td>
</tr>
<tr>
<td>• Refractory life threatening hypotension (secondary to vasodilatation and diminished aldosterone secretion).7</td>
</tr>
<tr>
<td>• QRS and ST changes on electrocardiography simulating acute myocardial infarction or conduction abnormalities.8</td>
</tr>
<tr>
<td>• Ventricular arrhythmia.9</td>
</tr>
<tr>
<td>• Raised plasma creatine phosphokinase (of skeletal muscle origin).9</td>
</tr>
<tr>
<td>• Improvement in cardiac output, peak velocity of blood flow, and exercise tolerance in asymptomatic hypocalcaemic patients on calcium replacement.10</td>
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</tbody>
</table>

Learning point

- Suspect hypocalcaemic cardiomyopathy in a patient presenting with thick tongue (or other manifestations of tetany) and unexplained cardiac failure.

Massive pleural effusion

Q1: What is the most probable cause for the massive pleural effusion?
The most probable diagnosis is pancreaticopleural fistula due to chronic alcoholic pancreatitis.

Q2: How should the diagnosis be confirmed?
The diagnosis is based on a high index of suspicion in patients suffering from chronic pancreatitis and pleural effusion. The diagnosis is usually based on a triad of1:

1. A massive and recurrent pleural effusion (fig 1; p 536).
2. An extremely high pancreatic isoamylase level in pleural fluid (in this case it was 4771 IU/l at admission and rose to 25190 IU/l five days later).
3. An exudative pleural effusion with protein content above 30 g/l (in this case it was 56 g/l).

The diagnosis is usually confirmed by computed tomography, or on endoscopic retrograde cholangiopancreatography (ERCP), which may show the fistula connection to the pleural cavity. The sensitivity of the computed tomography is enhanced if undertaken immediately after ERCP. Contrast injection into the pleural collection may also be used to image the fistula tract. In our case ERCP failed to opacify the pancreatic duct due to tight stricture but revealed a benign stricture due to chronic pancreatitis at the distal end of common bile duct, which was stented during the procedure.

Q3: What would be the differential diagnosis?
The commonest differential diagnoses include:
1. Pleural effusion due to acute pancreatitis. The effusion is usually small, self-limiting, and the pancreatic isoamylase level rarely exceeds 4000 IU/l.2 9
2. Pleural effusions are also seen with a range of malignancy, most commonly arising from lung, breast, and ovarian cancers. Such effusion generally contains salivary isoamylase with a low concentration of only 200–400 IU/l.7
3. The pleural collection in oesophageal perforation also contains salivary isoamylase and food particles. The diagnosis can usually be confirmed radiologically with a contrast swallow.

Q4: What are the options for treatment?
The treatment of pancreaticopleural fistula remains controversial. Once the diagnosis has been confirmed, usually by pleural fluid amylase and protein elevation, the management can be either conservative or operative. Initial conservative measures have a considerable support in the literature.2 9

The principles of conservative treatment include:
1. Correction of fluid and electrolytes.
2. Maintenance of adequate nutrition with enteral feeding but total parenteral nutrition may be required for patients with malabsorption and ongoing catabolic status.
3. Adequate drainage of pleural cavity with multiple thoracocenteses or tube thoracostomy.
4. Early treatment of infection using an appropriate antibiotic, together with drainage of abscess, percutaneously or surgically, if required to prevent the development of sepsis.
5. Octreotide is a long acting synthetic analogue of somatostatin. It inhibits pancreatic exocrine and endocrine secretion and relaxes intestinal musculature. As an adjuvant to standard conservative fistula management it reduces fistula output, but whether it shortens
the time for fistula closure remain to be proved by a well designed comparative study.10 11 Approximately 40%–60% of fistulas close spontaneously when the principles of conservative management are meticulously followed. It is emphasised, however, that surgery may be required for underlying pancreatic disease, in this regard close surveillance of these patients is necessary.1 12

In cases where fistula closure is not achieved with conservative treatment, an emerging role for ERCP has become evident. Pancreatic duct stricture is frequently found in a patient with pancreaticopleural fistula and successful results have been reported for fistula closure after endoscopic placement of stent. Transpapillary pancreatic duct stenting may remove the back pressure effect of stricture, stone and sphincter of Oddi, thus improving pancreatic duct drainage and enhance fistula closure. Long term follow-up is needed before its role can be more accurately defined.11 12

Surgical treatment is indicated when non-operative management fails and in the presence of life threatening complications. The site of the fistula and presence of pancreatic duct stricture13 determine the nature of the surgery. Hence the importance of preoperative evaluation with computed tomography and ERCP to define pancreatic duct anatomy. If ERCP is unsuccessful, operative panreatography should be performed at the time of surgery. This can be either by cannulating the ampulla through a duodenotomy, or by a retrograde technique after amputating the tail of the gland.1

Surgery is generally safe and effective.7 Distal pancreatic resection is indicated when the pancreaticopleural fistula arises from the body or tail of the pancreas, provided the proximal pancreatic duct is patent. Internal drainage by Roux-en-Y pancreaticojejunostomy or pseudocystojejunalostomy is generally indicated for fistula arising, respectively, from the head of pancreas and in presence of a large pseudocyst not amenable to resection.1 7 13 15 16

In chronically ill patients who represent a high anaesthetic risk and whose fistula did not respond to conservative treatment, a short course of radiotherapy may be considered.14

Discussion
Pancreaticopleural fistula is a rare complication of chronic pancreatitis and occurs in fewer than 1% of patients after pancreatitis and around 3% of patients with a pancreatic pseudocyst.7 15 Chronic alcoholic pancreatitis is the commonest cause of pancreaticopleural fistula, reported in up to 80% of cases. The typical patients are young male alcoholics.1 3 18 Pancreaticopleural fistula is associated with a substantial mortality of 5%–10%, primarily from sepsis.2 18

Pancreaticopleural fistula occurs when the pancreatic duct or one of its branches is disrupted by chronic inflammation. The resulting leakage of pancreatic fluid may communicate with the pleural cavity to form a fistula with subsequent pleural effusion (usually left sided).1 13

The clinical manifestation is often misleading, since about 48% of patients do not have a clinical history of pancreatic disease. Moreover, patients with pancreaticopleural fistula present more commonly with chest than abdominal symptoms due to the large size of the pleural effusion and the indolent nature of their pancreatic disease.2 3 17

Chest symptoms are variable; patients present most commonly with dyspnoea, wheezing, and coughing.

Abdominal symptoms are absent in 18% of patients but epigastric pain radiating to the back is commonly seen.7 Postprandial pain, weight loss, and abdominal distention due to ascites may also be observed. Pericardial effusion and cardiac tamponade have also been reported. Some patients develop subcutaneous fat necrosis producing white nodule lesions on the trunk or the lower limb.2 3

Final diagnosis
Pancreaticopleural fistula secondary to chronic alcoholic pancreatitis.

References
Siblings with multiple soft tissue calcifications

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