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Self-assessment

QUESTION

A 14-year-old girl presented to A&E with acute abdominal pain and vomiting. Questioning uncovered a history of thirst, polyuria, lethargy and malaise, increasing over the previous few weeks. This had led to her missing several weeks of schooling. One year previously, she had been given a diagnosis of Osgood–Schlatter's disease after presenting with bilateral knee pain. She had improved with physiotherapy but was still troubled by frequent bone pains. She had reached all developmental milestones as expected and had been otherwise well. Her paternal uncle was diabetic, but there was no other family history of note.

On examination, this was a slim girl who appeared mildly dehydrated. Her abdomen was soft and non-tender with normal bowel sounds and no masses. She was afebrile, and there were no other relevant findings.

No surgical cause could be found for her symptoms. She was normoglycaemic on both bedside and laboratory blood glucose analysis (5.4 mmol/l, reference fasting range 3.4–5.5 mmol/l), and a urine dipstick test showed protein+, blood+ and ketones negative.

Blood testing revealed these values (reference range in brackets):

- Na 148 mmol/l (135–145 mmol/l);
- K 3.7 mmol/l (3.5–5.3 mmol/l);
- urea 8.6 mmol/l (2.0–6.0 mmol/l);
- creatinine 85 μmol/l (30–90 μmol/l);
- total Ca^{2+} 2.92 mmol/l (2.15–2.55 mmol/l);
- PO_4 1.06 mmol/l (1.0–1.8 mmol/l);
- alkaline phosphatase 170 IU/l (100–400 IU/l);
- albumin 25 g/l (24–48 g/l).

Question 1

What is this girl's calcium level when corrected for serum albumin (corrected calcium reference range 2.2–2.7 mmol/l)?

a. 3.22 mmol/l
b. 3.54 mmol/l
c. 2.85 mmol/l
d. 3.85 mmol/l
e. 4.22 mmol/l.

Question 2

Which of the following statements about calcium homeostasis is *incorrect*?

a. Approximately 45% of serum calcium is bound to protein.
b. Parathyroid hormone stimulates bone resorption via its actions on osteoblasts.
c. Activated vitamin D inhibits the enzyme 1α-hydroxylase.
d. The daily calcium requirement for a teenage girl is 800 mg per day.
e. Wholemeal bread increases the dietary calcium absorption.

Question 3

What is your first-line treatment for this girl's symptomatic hypercalcaemia?

a. Sodium bicarbonate infusion
b. 0.9% saline infusion
c. Oral prednisolone
d. Bisphosphonate infusion
e. Furosemide.

The girl responds well to your treatment and is admitted to the ward for further investigation. The following results become available over the next 2 days:

- an intact parathyroid hormone level of 112 ng/l (reference range 3–48 ng/l);
- a 24-h urinary calcium of 6.1 mmol (reference range 2.5–7.5 mmol per 24 h).

The abnormalities persisted on repeated testing.

Question 4

Given the above information, which of the following is the most likely cause of her symptoms?

a. Chronic renal failure
b. Milk-alkali syndrome

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c. Parathyroid adenoma
d. Malabsorption
e. Sarcoidosis.

Question 5

If, after exploring this girl's family history, you found that her father had intractable stomach ulcers and her older sister was having trouble conceiving owing to a pituitary prolactinoma, which of the following would you have to consider?

a. Wermer's syndrome
b. DiGeorge syndrome
c. Sipple's syndrome
d. Williams syndrome
e. Familial hypocalciuric hypocalcaemia.

It was decided that the girl would need imaging tests to localize a potential focus of excessive parathyroid hormone secretion.

Question 6

Which of the following is *not* a recognized way of locating a parathyroid adenoma prior to surgery?

a. Subtraction ^{99}Tch (pertechnate) and ^{201}Th (thallium chloride) scintigraphy
b. Metaiodobenzylguanidine (MIBG) scanning
c. Preoperative methylene blue
d. Ultrasound scanning
e. ^{99m}Tc-sestamibi scanning.

Question 7

The girl underwent scanning using a radiolabelled tracer protein, the result of which is illustrated in Fig. 1. What does this show?

a. A globally increased uptake of tracer in the thyroid gland, suggesting co-existing thyrotoxicosis.
b. Persistent activity in the submandibular region, suggesting ectopic parathyroid tissue.
c. Failure of tracer washout on the right, suggesting a right inferior parathyroid adenoma.
d. The scans cannot be interpreted without delayed 24-h images for comparison.
e. None of the above.

Our patient was admitted for cervical exploration through a collar incision. The thyroid gland was mobilized, and a large 725 mg (reference weight 20–40 mg) parathyroid adenoma was excised.

Postoperatively, she developed tingling and stiffness in her hands. Her corrected calcium level was 2.03 mmol/l (reference range 2.2–2.7 mmol/l), and she was commenced on oral calcium supplements. She was normocalcaemic (2.27 mmol/l) at discharge on the fourth postoperative day and was able to stop her calcium supplements soon after.

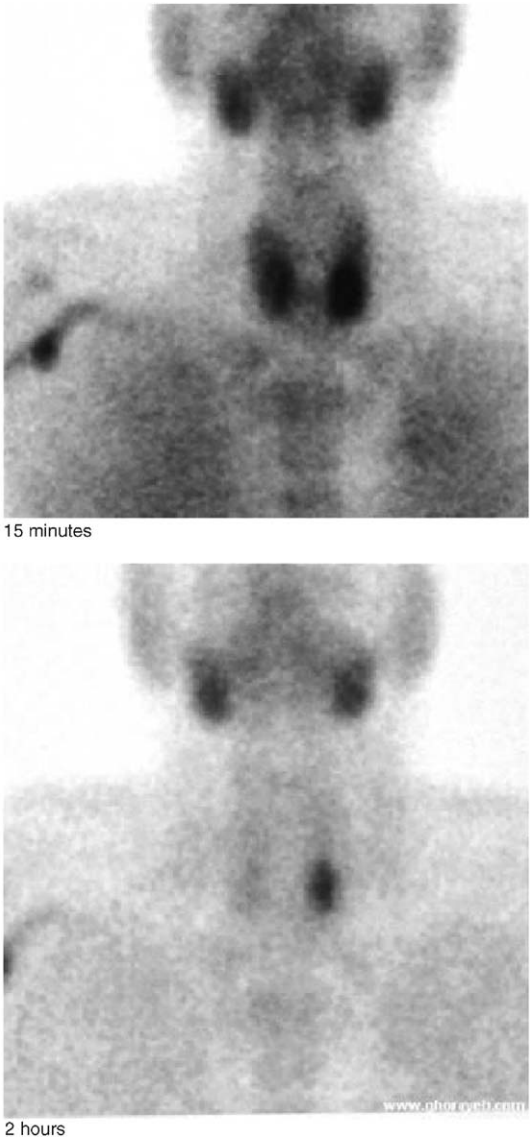

Figure 1 Imaging study. (Reproduced from www.ghorayeb.com, with kind permission of Bechara Y. Ghorayeb, MD, Clinical Associate Professor of Otolaryngology, University of Texas Medical School, Houston, Texas, USA.)

Question 8

Which of these is the most common complication of surgery for primary hyperparathyroidism?

a. Failure to remove the hyperfunctioning gland
b. Thyrotoxic storm
c. Recurrent laryngeal nerve palsy
d. Transient postoperative hypocalcaemia
e. Pneumothorax.

ANSWERS

Answer 1

a. 3.22 mmol/l.

On average, only around 1% of the body's calcium is found in the plasma and body fluids. Here it exists in three forms: ionized (45%), bound to proteins such as albumin (45%) and complexed to anions such as phosphate (10%). The protein-bound fraction is 80% bound to albumin and 20% bound to other proteins, including globulin. As a result, the total calcium level is more difficult to interpret if the patient's serum albumin level is abnormal. Various formulae exist to derive a calculated total calcium value if the patient has a normal albumin (in this age group, 40 g/l is acceptable).

A standard formula would be:

$$\text{Corrected calcium (mmol/l)} = \text{Total calcium (mmol/l)} + [40 - \text{albumin(g/l)}] \times 0.02.$$

Using our patient's data:

$$\text{Corrected calcium} = 2.92\,\text{mmol/l} + [40 - 25\,\text{g/l}] \times 0.02 = 3.22\,\text{mmol/l}.$$

Remember, however, that it is the ionized calcium that governs the biochemical effects. This is influenced not by albumin level but by other factors, including pH.

Answer 2

e. Wholemeal bread increases dietary calcium absorption.

Calcium is available in milk and dairy products, as well as in fortified white and brown flour. It is also well absorbed from vegetables such as broccoli. Absorption is, however, reduced in the presence of phytates, which are present in wholegrain cereals, unleavened bread and pulses. Oxalates in spinach and rhubarb also impair absorption. Mature osteoclasts do not appear to have parathyroid hormone receptors, and bone resorption is thought to be mediated through osteoblast intermediaries with the support of stromal cells.[1] Activated vitamin D inhibits the enzyme 1α-hydroxylase via negative feedback mechanisms. The recommended calcium intake for a teenage girl is 800 mg per day; reference nutrient intake levels vary according to age.[2]

Answer 3

b. 0.9% saline infusion.

Most patients with symptomatic hypercalcaemia are volume-depleted so, if possible, the patient should be weighed and then given 0.9% saline intravenously for rehydration. Once this has been achieved, furosemide can be used to induce a diuresis. Magnesium, potassium and fluid balance must be carefully monitored. All contributory drugs and infusions should be stopped if possible, and the cause investigated and treated. Steroids have been used in some settings, and in certain situations bisphosphonates such as alendronate have been employed to treat paediatric hypercalcaemia.[3]

Answer 4

c. Parathyroid adenoma.

The principal abnormalities in the girl's blood tests are a high calcium with an inappropriately high parathyroid hormone level; this suggests a loss of feedback inhibition of the parathyroid glands. In this case, primary hyperparathyroidism (adenoma, hyperplasia or hypertrophy of the chief cells in the parathyroid glands) is a more likely cause than tertiary hyperparathyroidism (autonomous gland functioning after chronic hypocalcaemia) because the girl does not have a history of a previous significant illness. Parathyroid adenoma accounts for around 90% of cases of primary hyperparathyroidism[4] but can also be caused by hyperplasia or even carcinoma. Secondary hyperparathyroidism (e.g. malabsorption) is associated with a low-normal calcium concentration. Hypercalcaemia secondary to sarcoidosis or excessive calcium ingestion (milk-alkali syndrome) would show suppressed parathyroid hormone.

Answer 5

a. Wermer's syndrome

Primary hyperparathyroidism is rare (with a prevalence of approximately 25 per 100 000). The most common cause of primary hyperparathyroidism is a solitary sporadic parathyroid adenoma. When, however, there is the possibility of a familial abnormality, syndromes such as multiple endocrine neoplasia (MEN) I (Wermer's syndrome), MEN IIA (Sipple's syndrome) and familial non-MEN hyperparathyroidism should also be considered. In MEN I, the parathyroid glands are the most commonly affected glands, being involved in over 90% of patients. In addition, pancreatic islet cell tumours (gastrinomas causing Zollinger–Ellison syndrome and the father's stomach ulcers in this case), pituitary tumours (prolactinoma causing reduced fertility in her sister), adrenal adenomas and thyroid adenomas may arise. MEN IIA is characterized by medullary thyroid carcinoma, phaeochromocytoma and hyperparathyroidism (20–30%).[5]

DiGeorge syndrome and Williams syndrome do not cause hyperparathyroidism, and familial hypocalciuric hypercalcaemia would be associated with a low 24-h urinary calcium excretion.

In this featured case study, the family history was actually negative except for type II diabetes in the girl's uncle. Her prolactin, 24-h urinary catecholamines, insulin, calcitonin, thyroid function and growth hormone level were all within normal limits. An abdominal ultrasound did not demonstrate any renal or pancreatic abnormality. She did not have MEN.

Answer 6

b. Metaiodobenzylguanidine (MIBG) scan.

Metaiodobenzylguanidine (MIBG) scans are used to detect and localize phaeochromocytomas rather than parathyroid adenomas.

Abnormal parathyroid glands can be identified by a variety of techniques. Subtraction scintigraphy utilizes the different uptakes of ^{201}Th (thallium chloride) and ^{99}Tch (pertechnate). ^{201}Th is taken up by both the thyroid and hyperfunctioning parathyroids, but only the thyroid takes up ^{99}Tch. Digital subtraction of the ^{99}Tch scan from the ^{201}Th scan therefore

leaves just the parathyroid image. ^{99m}Tc-sestamibi scanning has largely replaced this form of subtraction scanning.

Sestamibi is a large synthetic molecule of the isonitrile family and can be labelled with technetium. Initially (at a 15-min scan), it is taken up by the thyroid and the parathyroids. Later (at a 2-h scan), it has washed out of the thyroid, but as it takes longer to wash out of the abnormal parathyroid gland, the parathyroid adenoma remains visible. ^{99m}Tc-sestamibi can have a sensitivity of up to 92%[6] and can be used alone or with ^{123}I^{99}Tch. Radiopharmaceutical scans also highlight ectopic and intrathoracic adenomas, which may be missed using surgical exploration alone.

Ultrasonography can detect enlarged parathyroid glands in approximately 77% of cases but is less sensitive for ectopic glands.[7] Combining sestamibi scanning and high-resolution ultrasound increases their accuracy.[8]

Intraoperative methylene blue infusion stains parathyroid adenomas dark blue-purple, whereas normal glands stain a paler green shade.

Answer 7

e. None of the above.

This scan is suggestive of a *left* inferior parathyroid adenoma. Fifteen minutes after administration of the radioisotope, uptake is visible in the thyroid gland. Two hours later, the uptake is concentrated in the left inferior region of the neck, after it has 'washed out' from the thyroid gland. This corresponded with the results of a high-resolution ultrasound of the girl's neck, which located a $6 \times 22 \times 4$ mm nodule posterior to the lower pole of the left lobe of the thyroid. It had appearances consistent with those of a parathyroid adenoma.

Answer 8

d. Transient postoperative hypocalcaemia.

Surgery is the definitive treatment for primary hyperparathyroidism, 3% of operations being carried out on children and adolescents.[9] Cure is possible in over 95% of individuals, and multiglandular disease is the major cause of surgical failure. For most patients, it is sufficient to remove the one abnormal gland, but those with multiglandular hyperplasia require the excision of 3.5 or 4 glands with or without autotransplantation.

Removal of the adenomatous parathyroid tissue can be confirmed by intraoperative frozen section or intact parathyroid hormone assay. Owing to its short half-life (2–5 min), a parathyroid hormone measurement taken 10 min after suspected gland removal can confirm removal of the adenoma. A 50% reduction in intraoperative intact parathyroid hormone or normalization of the level is predictive of postoperative normocalcaemia.[10]

The operation is generally well tolerated. Complications include transient hypocalcaemia (biochemical in up to 25%, symptomatic in up to 11%, influenced by the surgical approach)[11] and recurrent laryngeal nerve injury (0.8%).[12] Patients should be warned about this, as well as about failure to correct the hypercalcaemia (estimates vary between approximately 1% and 6%), infection, scarring and bleeding. Transient hypocalcaemia can be treated in the short term with calcium and vitamin D supplementation; it usually recovers spontaneously. Subtotal or total parathyroidectomy with autotransplantation is associated with a higher rate of permanent hypoparathyroidism, requiring lifelong supplements. Pneumothorax is not usually a complication of this operation. Thyrotoxic storm is traditionally associated with hyperthyroidism rather than hyperparathyroidism.

Learning points

Primary hyperparathyroidism is rare in children, with estimates in the region of 2–5 per 100 000 individuals. The diagnosis of is often delayed and is usually suspected from symptoms of hypercalcaemia. The long-term effects are potentially serious (Box 1).

Box 1 Potential consequences of prolonged hyperparathyroidism.

Musculoskeletal
- Bone pain and tenderness
- Reduced bone density
- Osteitis fibrosa et cystica with risk of pathological fracture
- Pseudogout
- Hypotonicity of the muscles
- Proximal myopathy

  Ten per cent of patients have clinical evidence at presentation, and 20% have biochemical evidence. In growing children, primary hyperparathyroidism can cause crippling deformities.

Gastrointestinal
- Peptic ulceration (5–10%)
- Acute and chronic pancreatitis
- Nausea and vomiting
- Constipation

Renal
- Renal calculi (up to 50%)
- Nephrocalcinosis
- Progressive chronic renal failure
- Dehydration
- Polydipsia and polyuria

Neurological
- Fatigue
- Behavioural disturbance
- Depression
- Dementia
- Focal neurological lesions
- Band keratopathy

Cardiovascular
- Hypertension
- Calcification of the vessel walls
- Shortening of the QT interval

Symptoms occur in most affected children and include weakness, irritability, hypotonia, poor feeding, weight loss, polyuria, polydipsia, constipation and vomiting. Prompt surgical treatment can avoid the severe complications of prolonged hypercalcaemia.

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