Ehlers-Danlos syndrome with parathyroid adenoma for excision

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Abstract

Ehlers-Danlos syndrome (EDS) consists of a group of connective tissue disorders characterised by hyperelasticity of the skin and hypermobile joints. Parathyroid adenoma results in increased parathyroid hormone secretion. We report the case of a 20-year-old male patient with EDS and parathyroid adenoma, who underwent surgery to excise the tumour. A thorough preoperative evaluation, stabilisation, and necessary precautions and monitoring during the intraoperative period, ensured an uneventful postoperative period.

Introduction

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a connective tissue disorder characterised by hyperelasticity of the skin and hypermobile joints. Approximately 11 types of EDS have been identified, based on the extent to which the skin, joints, and other tissues, are affected. All forms of EDS cause signs and symptoms of joint hypermobility, skin fragility or hyperelasticity, easy bruisability, musculoskeletal abnormalities, and susceptibility to osteoarthritis.[1]

Skin changes vary from thin and velvety skin, to skin that is either dramatically hyperextensible ("rubber person" syndrome) or easily torn, or scarred. Patients with classical EDS develop characteristic "cigarette paper" scars. Patients with EDS type IV have alteration in type III collagen, which predisposes them to sudden death from spontaneous rupture of the large blood vessels, or hollow viscera. The gastrointestinal tract, uterus and vasculature, are particularly well endowed with type III collagen, accounting for these fatal complications. The ocular-scoliotic type of EDS (type VI) is characterised by scoliosis, ocular fragility, and keratoconus. The eye may rupture with minimal trauma, and kyphoscoliosis can cause respiratory impairment. There is increased incidence of pneumothorax, and dilation of the trachea in EDS. Mitral regurgitation and cardiac conduction abnormalities are occasionally seen. Patients may exhibit extensive ecchymoses, with only minimal trauma, though a specific coagulation defect has not been identified.[2]

Patients with type IV EDS, and members of their families, should be evaluated at regular intervals for early detection of aneurysms, but surgical repair may be difficult because of friable tissues. Women with type IV EDS should be counselled about the increased risk of uterine rupture, bleeding, and pregnancy complications.

Due to overlapping signs and symptoms, many patients and families with EDS features cannot be assigned to any of the defined types. The diagnosis is based on clinical criteria. Biochemical assays and gene analyses for known molecular defects in EDS are difficult and time consuming, but the tests are particularly useful for the diagnosis of vascular-type IV EDS, with its grave prognosis.

Hyperparathyroidism

The four parathyroid glands are located behind the upper and lower poles of the thyroid gland, and produce parathyroid hormone (parathormone or PTH), a polypeptide hormone. PTH is released into the systemic circulation by a negative feedback mechanism that depends on the plasma calcium concentration.

Hypocalcaemia stimulates the release of PTH, whereas hypercalcaemia suppresses both the synthesis and release of this hormone. The ionised fraction of blood calcium is the important determinant of hormone secretion.[3] PTH maintains normal plasma calcium concentrations (4.5-5.5 mEq/l) by promoting the movement of calcium across the three interfaces, namely the gastrointestinal tract, renal tubules and

bone. It stimulates bone resorption, inhibits renal excretion of calcium, and increases conversion to active vitamin D, three conditions that lead to hypercalcaemia. It increases the tubular reabsorption of calcium and magnesium, and decreases the tubular reabsorption of phosphate, sodium, bicarbonate, potassium and amino acids. PTH activates the adenylate cyclase system by binding with receptor sites in the renal cortex. It leads to an increase in urinary excretion of cyclic adenosine monophosphate (cAMP).[4]

Hyperparathyroidism is present when the secretion of PTH is increased. Serum calcium concentrations may be increased, decreased or unchanged. Hyperparathyroidism can be classified as primary, secondary and ectopic.

Primary hyperparathyroidism results from excessive secretion of PTH due to a benign parathyroid adenoma, carcinoma of a parathyroid gland, or hyperplasia of the parathyroid glands. Benign parathyroid adenomas are responsible for primary hyperparathyroidism in approximately 90% of patients, while carcinoma of the parathyroid gland is responsible for less than 5% of affected patients.[5] Hyperplasia usually implicates all four parathyroid glands, although not all glands may be enlarged to the same degree. Hyperparathyroidism that is due to an adenoma or hyperplasia is the most common presenting symptom of multiple endocrine neoplasia 1 syndrome.

Secondary hyperparathyroidism reflects an appropriate compensatory response of the parathyroid glands to secrete more PTH in disease conditions that produce hypocalcaemia, such as chronic renal disease. Ectopic hyperparathyroidism (humoral hypercalcaemia of malignancy) is due to secretion of PTH or PTH-related peptide by tissues other than the parathyroid glands, and it is found in patients with carcinoma of the lung, carcinoma of the breast, and lymphoproliferative diseases.

A few patients develop severe manifestations of secondary hyperparathyroidism, including hypercalcaemia, pruritus, extraskeletal calcifications and painful bones, despite aggressive medical therapy to suppress the hyperparathyroidism. PTH hypersecretion that is no longer responsive to medical measures has been referred to as tertiary hyperparathyroidism. This state of severe hyperparathyroidism in patients with renal failure requires parathyroidectomy.

Signs and symptoms

Signs and symptoms include:
- Somnolence, psychosis, and decreased pain and vibration sense
- Skeletal muscle weakness and hypotonia

- Vomiting, abdominal pain, peptic ulcer disease and pancreatitis
- Polyuria, polydypsia, decreased glomerular filtration rate (GFR), renal stones and oliguric renal failure
- Anaemia
- Systemic hypertension
- Electrocardiogram (ECG) changes: a prolonged PR interval and short QT interval[6]
- Osteitis fibrosa cystica, pathological fractures and collapse of vertebral bodies
- X-ray findings: generalised osteopenia, subcortical bone resorption in the phalanges and distal end of clavicles, and appearance of bone cysts.

Diagnosis

Hypercalcaemia (serum calcium concentration > 5.5 mEq/l and ionised calcium concentration > 2.5 mEq/l) is the hallmark of hyperparathyroidism. Urinary excretion of cAMP is increased in patients with primary hyperparathyroidism. The most useful confirmatory test for hyperparathyroidism is a radioimmunoassay for PTH. In the absence of renal insufficiency, the combination of hypercalcaemia and elevated serum PTH concentration most accurately predicts the diagnosis of primary hyperparathyroidism.[7]

Treatment

Primary hyperparathyroidism and associated hyper-calcaemia are treated by medical means initially, followed by definitive surgical removal of the diseased, or abnormal, portions of the parathyroid glands.

Medical management

Intravascular fluid volume may be depleted by vomiting, polyuria, and urinary loss of sodium. Restoration of the intravascular volume, augmentation and excretion of urinary sodium (with saline infusion), and the administration of diuretics (furosemide is commonly used), generally increase urinary calcium excretion substantially. Infusion rates of 200-400 ml/hour preoperatively are commonly used, but central venous pressure monitoring is needed to avoid fluid overload, especially since many patients have compromised cardiac contractility. Ringer's lactate is not suggested because it contains calcium.

The calcium-lowering effect of loop diuretics (furosemide 40-80 mg intravenously every two to four hours), is useful here, along with saline infusion, but only after the intravascular fluid volume has been optimised. The addition of loop diuretics to saline hydration increases calcium excretion only if the saline infusion is adequate to restore the intravascular fluid volume necessary for delivery of calcium to the renal tubules. The goal is a daily urinary

output of three to five litres. Thiazide diuretics are not administered, as these drugs aggravate hypercalcaemia by enhancing renal tubular reabsorption of calcium. Phosphate should be given to correct hypophosphataemia because it decreases calcium uptake into bone, increases calcium excretion, and stimulates bone breakdown.[8] Hydration and diuresis, accompanied by phosphate repletion, suffice in the management of most hypercalcaemic patients.

Other measures to decrease resorption of bone include the bisphosphonates pamidronate sodium (90 mg intravenously) and zoledronate (4 mg intravenously), salmon calcitonin (100-400 units nasally every 12 hours), plicamycin or mithramycin (15-25 µg/kg intravenously) and cinacalcet (30 mg orally once daily).[9,10] Bisphosphonates act as potent inhibitors of osteoclastic bone resorption. The effectiveness of bisphosphonates allows surgery to be performed under elective conditions, rather than as an emergency in unstable hypercalcaemic patients. Haemodialysis, as well as calcitonin, can also be used to lower serum calcium concentrations promptly, but the effect of calcitonin is transient. The toxic effects of plicamycin (thrombocytopenia, hepatotoxicity and nephrotoxicity) limit its use.

Glucocorticoid administration reduces the level of calcium in the blood, through an effect on gastrointestinal absorption in many other conditions that cause hypercalcaemia, but not in primary hyperparathyroidism usually. The new calcimimetic cinacalcet is indicated for the treatment of secondary hyperparathyroidism in chronic kidney disease patients on dialysis, and the treatment of elevated calcium levels (hypercalcaemia) in patients with parathyroid carcinoma.

Surgical management

Definitive treatment of primary hyperparathyroidism is the surgical removal of the diseased, or abnormal, portions of the parathyroid glands. Symptomatic primary hyperparathyroidism is usually treated surgically in those younger than 50 years, or with serum calcium levels more than 1 mg/dl above the upper limit of normal, a 30% or greater reduction in the glomerular filtration rate (GFR), or severe bone demineralisation. If the patient refuses surgery, or if other illnesses make surgery inadvisable, medical management with cinacalcet makes medical management much more feasible.

Successful surgical treatment is reflected by normalisation of serum calcium concentrations within three to four days, and a decrease in the urinary excretion of cAMP. Postoperatively, the first potential complication is hypocalcaemic tetany. The hypomagnesaemia that occurs postoperatively aggravates the hypocalcaemia, and renders it refractory to treatment. Hyperchloraemic metabolic acidosis, in association with

deterioration of renal function, may occur transiently after parathyroidectomy.

Case report

A 20-year-old man, a known case of EDS with right parathyroid adenoma, was booked for excision of the tumour. He was possibly EDS type VI, but he lacked some of the features, such as keratoconus. The patient was healthy until five months prior, when he began to experience certain symptoms. He experienced chest pain, especially over the ribs, more at the back, and breathlessness on exertion. He also complained of pain in the upper abdomen, and early satiety. He had a history of tiredness and weight loss (~8 kg) over five months. He had noticed a decrease in his height (~12 cm) due to excessive curvature of the spine.

On examination, the patient had Grade II digital clubbing, long slender fingers, and hyperelastic skin. His vitals were stable. He had kyphoscoliosis of the thoracic spine, along with pigeon chest deformity, and tenderness over the posterior end of the ribs. Cardiovascular and per abdomen examination were unremarkable. Airway examination did not reveal any abnormality.

Laboratory investigations

The laboratory investigation results are summarised in Table I

Table I: Laboratory results

Haemoglobin: 13.2 g/dl
Total white blood cell (WBC) count: 10.200/µl
Differential count: Neutrophils 44%, lymphocytes 45%, monocytes 8%, eosinophils 3%
Random blood sugar level: 90 mg/dl
Blood urea: 14 mg/dl
Serum creatinine: 0.6 mg/dl
Serum sodium:138 mEq/l
Serum potassium: 4.8 mEq/l
Serum chloride:110 mEq/l
Serum calcium: 6.3 mEq/l
Plasma PTH: > 1 900 pg/ml (normal value is 11.1-79.5 pg/ml)
Serum calcitonin: 3.53 pg/ml (normal is up to 18.2 pg/ml)
Bleeding time: 1 minute,1 second
Clotting time: 5 minutes.

Thyroid function tests were normal. Pulmonary function tests revealed a mild restrictive disease pattern. ECG showed right bundle branch block (RBBB) and right axis deviation. The echocardiogram was normal. A chest X-ray (posteroanterior view) revealed severe osteopenia of the bones, deformity of multiple ribs, and kyphoscoliosis of the thoracic spine. The lung fields were clear, and cardiac size was normal. These findings were consistent with hyperparathyroidism.

Computed tomography of the neck showed a well-defined rounded lesion below the inferior pole of the right lobe of

the thyroid gland, suggestive of parathyroid adenoma, and severe osteoporotic changes in the bones, due to hyperparathyroidism. Ultrasonography of the neck revealed a well-defined hypoechoic oval lesion inferior to the right lobe of the thyroid gland, suggestive of parathyroid adenoma.

The technetium (Tc) 99m sestamibi scan showed a focal and persistent active spot at the lower pole of the right lobe of the thyroid gland, consistent with parathyroid adenoma. Magnetic resonance imaging of the thoracic spine depicted demineralisation of the vertebrae and ribs, osteoporotic collapse of the D7 vertebra, with kyphoscoliotic deformity in the upper thoracic spine, fracture of the lateral aspect of multiple ribs, and osteolytic lesions of the ribs and pelvic bones. These findings were suggestive of primary hyperparathyroidism generalised osteitis fibrosa cystica.

The patient was diagnosed as a case of EDS, with right parathyroid adenoma with kyphoscoliosis of the thoracic spine.

Anaesthetic management

Preoperatively, normocalcaemia was achieved with intravenous saline hydration and intravenous furosemide therapy. The patient was carefully positioned on the operating table, and monitors were attached [non-invasive blood pressure (BP) cuff, SpO_2, ECG and $EtCO_2$]. Baseline vitals were noted: a pulse rate of 90/minute, BP of 110/70 mm Hg, and SpO_2 – 100%.

The patient was premedicated with intravenous ondansetron 4 mg, intravenous glycopyrrolate 0.2 mg, and intravenous fentanyl 2 µg/kg. After adequate preoxygenation, general anaesthesia was induced with intravenous thiopentone sodium (2.5%) 5 mg/kg, followed by intravenous vecuronium 0.1 mg/kg. Laryngoscopy was performed carefully, and orotracheal intubation was carried out with an 8.0-sized endotracheal tube, and the position of the tube was confirmed. Maintenance of anaesthesia was achieved by using N_2O and O_2, along with isoflurane. A further two doses of intravenous vecuronium (0.02 mg/kg) were administered with neuromuscular monitoring using a peripheral nerve stimulator. Two more doses of intravenous fentanyl (1 µg/kg) were administered.

The surgery lasted 120 minutes, during which the patient received 1 500 ml of normal saline. Blood loss during surgery was about 150 ml. Vitals were stable throughout the surgery. At the end of surgery, infiltration of the surgical wound was carried out with 10 ml of 0.25% bupivacaine. Reversal of the neuromuscular blockade was achieved with intravenous neostigmine 0.05 mg/kg, and intravenous

glycopyrrolate 0.01 mg/kg. The patient was extubated after confirming good ventilatory mechanics and good gag reflex, and after thorough oral suctioning. He was comfortable and his vitals were stable.

Postoperatively, the patient was shifted to the intensive care unit for observation. Serum calcium levels were checked regularly, and were found to be normal. He received intravenous paracetamol and tramadol for postoperative pain relief. He had an uneventful postoperative period.

Discussion

Management of anaesthesia in patients with EDS must consider the cardiovascular manifestations of this disease, and the propensity for these patients to bleed excessively. Avoidance of intramuscular injections, or instrumentation of the nose or oesophagus, is important, in view of the bleeding tendency. Care should be taken to avoid any trauma during laryngoscopy. Placement of an arterial, or central venous catheter, must be tempered by the realisation that haematoma formation may be extensive. Extravasation of intravenous fluids, due to a displaced venous cannula, may go unnoticed because of the extreme laxity of the skin. Maintenance of low airway pressure, during assisted or controlled mechanical ventilation, seems prudent, in view of the increased incidence of pneumothorax. Regional anaesthesia is not recommended because of the tendency of these patients to bleed and form extensive haematomas. Surgical complications include haemorrhage and postoperative wound dehiscence.

There is no evidence that any specific anaesthetic drug or technique is necessary in patients with primary hyperparathyroidism, who are undergoing elective surgical treatment of the disease. The most important aspect of preoperative preparation of these patients is the treatment of hypercalcaemia. One needs to be vigilant about various factors that might alter serum calcium levels. Preoperative preparation in urgent surgical interventions should focus on the potentially dangerous consequences of hyperparathyroidism only, such as hypercalcaemic crisis, or extreme hyperkalaemia.[11] It is important to correct malnutrition and low albumin levels in the preoperative period. Maintenance of adequate hydration and urinary output is important during perioperative management of hypercalcaemia.

If present, pre-existing systemic hypertension should be controlled. Optimal control of BP is known to cause reduction in mortality, and markedly improve cardiovascular prognosis. β blocker use in the preoperative preparation for general anaesthesia significantly increases cardiovascular stability, and decreases the frequency and severity of

haemodynamic disturbances during the surgical procedure. β blockers may also cause hypocalcaemia, and assist in blood pressure control.[12]

In the intraoperative period, the acid-base status requires special focus. The transfusion of large amounts of citrated blood may result in life-threatening hypocalcaemia. Intraoperative anaesthetic requirements might be decreased in patients with somnolence before anaesthesia induction. Ketamine is better avoided in patients with coexisting personality changes attributed to chronic hypercalcaemia.[5] In patients with coexisting renal dysfunction, cautious use of inhalational anaesthetics is recommended, as impaired urine-concentrating ability associated with polyuria and hypercalcaemia could be confused with anaesthetic-induced fluoride nephrotoxicity. Sevoflurane, one of the most preferred and used inhalation anaesthetics, should rather be avoided because of fluorides, although its harmful effect in patients with initial renal insufficiency has not been proved in most clinical studies.

Co-existing skeletal muscle weakness points to the possibility of decreased muscle relaxant requirements, whereas hypercalcaemia might be expected to antagonise the effects of non-depolarising muscle relaxants. In view of the unpredictable response to muscle relaxants, it is advisable to decrease the initial dose of these drugs, and to monitor the response at the neuromuscular junction using a peripheral nerve stimulator.[13] Monitoring the ECG for manifestations of adverse cardiac effects of hypercalcaemia is recommended, even though the QT interval may not be a reliable index of changes in serum calcium concentrations during anaesthesia.[14]

Theoretically, hyperventilation of the lungs is undesirable, as respiratory alkalosis lowers serum potassium concentrations, and leaves the actions of calcium unopposed. Nevertheless, alkalosis could also be beneficial by lowering ionised fractions of calcium.

Careful positioning of hyperparathyroid patients is important, because of the likely presence of osteoporosis and associated vulnerability to pathologic fractures. In the postoperative period, nonsteroidal anti-inflammatory drugs should be avoided for pain control, in case there is renal function impairment.[15]

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