Pitfalls in the management of hypocalcaemia: refractory hypocalcaemia after thyroidectomy not caused by postoperative hypoparathyroidism

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Abstract

A 29-year-old patient was admitted with tetany and severe hypocalcaemia despite treatment with high dose alphacalcidol and calcium. Six years earlier she was treated with subtotal thyroidectomy for non-toxic goitre in the Department of Surgery. Postoperatively she required replacement with 100 µg/day of L-thyroxin, but was lost to formal endocrine follow-up. Five years later she presented with non-specific abdominal discomfort and occasional diarrhoea. Examination revealed positive Chvostek's and Trousseau's signs, while plasma calcium, decreased to 1.8 mmol/l (ref. range: 2.2-2.55), was thought to be related to hypoparathyroidism caused by thyroidectomy. In view of slightly raised TSH the dose of L-thyroxin was gradually increased to 150 µg. Hypocalcaemia, however, failed to normalise, and in fact worsened, despite gradual increase in the dose of alphacalcidol, and denial of compliance problems with her medication. She was then admitted to hospital. The combination of low calcium, normal phosphate, iron-deficiency anaemia together with poor response to oral medication raised a possibility of malabsorption rather than a simple post-thyroidectomy hypoparathyroidism. Repeated gastroscopy was performed and demonstrated villous atrophy consistent with coeliac disease. Measurement of PTH concentrations of 63.6 pg/ml (ref. range: 15-65 pg/ml) confirmed the presence of functional parathyroids. She was started on a gluten-free diet. Her calcium levels are now normal and the dose of alphacalcidol is being decreased. In conclusions, hypocalcaemia after thyroidectomy cannot be automatically assumed to be caused by post-operative hypoparathyroidism and/or compliance problems. Other possible causes of hypocalcaemia should be considered and appropriately investigated.

Key words: hypocalcaemia, coeliac disease, hypoparathyroidism.

Case report

Initial presentation

A 29-year old female patient was admitted with tetany and severe hypocalcaemia despite treatment with high dose alphacalcidol (6 µg/day) and calcium (8.0 g/day).

Past medical history

Six years earlier she was treated with subtotal thyroidectomy for non-toxic goitre in the Department of Surgery. Postoperatively she required replacement with 100 µg/day of L-thyroxin but was lost to formal endocrine

Table I. Selected results of patient on admission

Parameter	Unit	Value	Reference range
Albumin adjusted calcium	mmol/l	1.18	2.2-2.55
PO_4	mmol/l	1.21	0.87-1.45
Mg	mmol/l	0.76	0.6-1.45
Urea	mg/dl	11	20-40
Creatinine	mg/dl	0.6	0.6-1.4
TSH	mIU/l	9.21	0.4-4
Total cholesterol	mg/dl	98	140-200
HB	g/dl	10.7	12-15
MCV	fl	68.3	78-93
Transferrin saturation	%	16	25-35
Urinary calcium	mmol/24 hours	0.26	2.5-6.25
Glucose	mg/dl	77	70-105
Urea	mg/dl	11	17-46
Creatinine	mg/dl	0.6	0.5-0.9
Alkaline phosphatase	IU/l	51	53-128
AlAT	IU/l	45	10-36
AspAT	IU/l	38	10-30
Total bilirubin	mg/dl	0.56	0.2-1.0

follow-up. Five years later she presented with non-specific abdominal discomfort and occasional diarrhoea. Investigations performed in the Department of Gastroenterology demonstrated microcytic anaemia (HB 9.8 g/dl, MCV 63 fl). Gastroscopy revealed gastritis and positive test for *Helicobacter pylori*. Eradication therapy (amoxicillin, clarithromycin, omeprazole) was prescribed and she was discharged on iron supplements without follow-up. Subsequently she was referred to the Endocrine Clinic because of continuing ill-health.

Examination

No obvious distress, no evidence of metacarpal shortening, heart rate 72 per minute, regular, blood pressure 110/70, clear lung fields. Positive Chvostek's and Trousseau's signs.

Initial investigations in endocrine outpatient clinic

Low plasma calcium of 1.8 mmol/l (ref range: 2.2-2.55) was thought to be related to hypoparathyroidism caused by thyroidectomy. In view of slightly raised TSH the dose of L-thyroxin was gradually increased to 150 µg. Hypocalcaemia, however, failed to normalise, and in fact worsened, despite gradual increase in the dose of alphacalcidol, and denial of compliance problems with her medication. She was then admitted to hospital. Investigations on admission are presented in Table I.

Further progress

The combination of low calcium, normal phosphate, iron-deficiency anaemia together with poor response to oral medication raised a possibility of malabsorption rather than a simple post-thyroidectomy hypoparathyroidism. Repeated gastroscopy and small-bowel biopsy were performed and demonstrated villous atrophy consistent with coeliac disease (Figure 1). Furthermore she had increased concentrations of antigliadin antibodies AGA-IgA 99.2 U/ml (ref. range <11 U/ml), AGA IgG 54.5 U/ml (ref. range <11 U/ml) and IgA class antiendomysial antibodies 1:40 U/ml consistent with coeliac disease.

Measurement of PTH concentrations of 63.6 pg/ml (ref range 15-65 pg/ml) revealed the presence of functional parathyroids. She was started on a gluten-free diet. Her calcium levels are now normal and the dose of alphacalcidol is being decreased (Table II).

Discussion

Postoperative hypoparathyroidism is the most common cause of chronic hypocalcaemia. This condition may occur after removal of all parathyroid glands or after interruption of the blood supply to the parathyroid glands during operation. The frequency of this complication is about 5%, increasing after total thyroidectomy or repeated surgery on thyroid remnant [1]. The frequency of accidental parathyroid gland removal has, however, decreased in recent years [2].

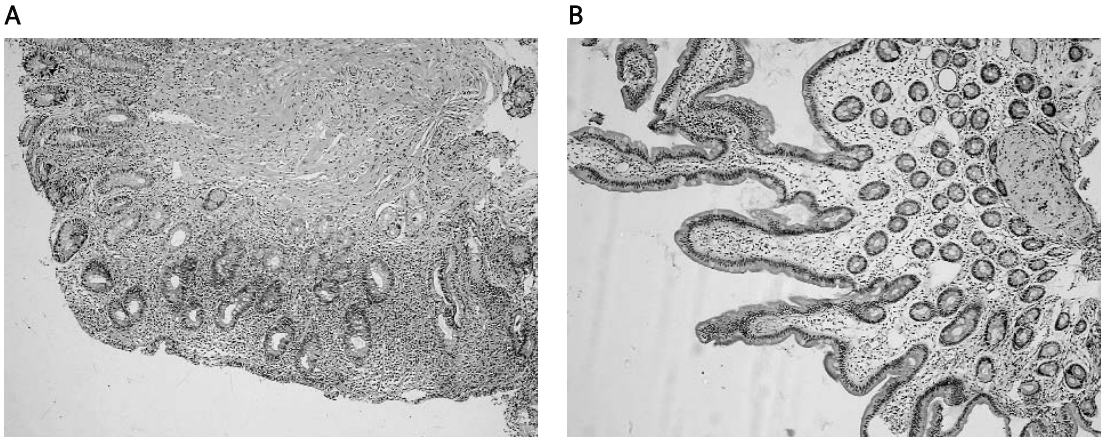

Figure 1. Normal small bowel biopsy with finger-like villi (A); small-bowel biopsy from our patient showing villous atrophy and hypertrophy of crypts (B)

Alphacalcidol or calcitriol together with calcium supplements, such as calcium carbonate, play the main role in the management of persistent hypocalcaemia. In the case of marked hypercalciuria thiazide diuretics are prescribed. A low-phosphate diet is recommended. The aim of treatment of hypoparathyroidism is to restore normal serum calcium level without significant hypercalciuria (risk of nephrolithiasis), so as to avoid hypocalcaemic complications as well as vitamin D intoxication at another extreme. Routine doses of alphacalcidol are seldom higher than 3 µg and calcium carbonate oscillates around 3.0 g/day [3].

Persistent hypocalcaemia during therapy requires further investigations. First, compliance problems should be excluded. Others causes of refractory hypocalcaemia include low concentration of magnesium, concomitant therapy with diuretics (frusemide), bisphosphonates, calcitonin, phosphates or anticonvulsants, chronic renal failure, renal tubular disorders, hepatobiliary or pancreatic disease and impaired gastrointestinal absorption.

Combination of low calcium and phosphate concentrations is characteristic for impaired gastrointestinal absorption; such changes were present in our patient. They were accompanied by anaemia with low iron concentration and low cholesterol level. Malabsorption also caused increased demand for L-thyroxin with higher TSH level.

The main mechanism of disturbances in Ca-P metabolism in coeliac disease is calcium malabsorption, which is primarily caused by villous atrophy and secondarily by coexisting vitamin D deficiency [4]. Impaired intestinal calcium absorption leads to secondary hyperparathyroidism, which is often present and may worsen the bone disease through increased bone turnover [5-7]. Our patient had only small spinal osteopenia, probably as a consequence of the lack of a significant increase of PTH concentration. In fact, PTH concentrations were around the upper limit of normal, despite the absence of hypomagnesaemia. Though treatment with alphacalcidol, albeit of limited efficacy in the setting of coexistent malabsorption, could have also limited the extent of PTH increase, the lack of significant secondary hyperparathyroidism, given the severity of hypocalcaemia, might indicate a limited parathyroid reserve. The cause of such a limited parathyroid reserve might be related to removal of some of her parathyroid glands during surgery,

Table II. Results of calcium and phosphate during therapy

	Albumin adjusted Ca (mmol/l)	Phosphate (mmol/l)	Treatment
On admission	1.05	1.19	Calcium carbonicum 6.0 Alphacalcidol 6.0 µg
After iv. calcium	1.56	1.46	Calcium carbonicum 6.0 Alphacalcidol 6.0 µg
Start of gluten-free diet	1.22	1.46	Calcium carbonicum 8.0 Alphacalcidol 6.0 µg
After one month	2.01	–	Calcium carbonicum 5.0 Alphacalcidol 4.0 µg
After four months	2.15	1.52	Calcium carbonicum 3.0 Alphacalcidol 3.0 µg

though there are also recent case reports about the coexistence of autoimmune hypoparathyroidism and coeliac disease. Patients with other endocrine diseases of autoimmune origin may also have concomitant coeliac disease [8]. For instance, coeliac disease is found in 2-5% of patients with type 1 diabetes mellitus or autoimmune thyroid disease.

The prevalence of coeliac disease is 1:340 among asymptomatic and presumably healthy people, so lack of overt symptoms does not exclude that disease [9]. So far we have, however, elected not to undertake any additional screening for coexistent autoimmune conditions in our patient, as it does not affect her clinical management at this point.

It should be stressed that in the case of malabsorption a proper diet is a crucial factor. First, we were unable to increase calcium concentration in spite of increasing doses of vitamin D and calcium. After introducing a gluten-free diet we could diminish doses of these drugs.

In conclusions hypocalcaemia after thyroidectomy cannot be automatically assumed to be caused by post-operative hypoparathyroidism and/or compliance problems. Other possible causes of hypocalcaemia should be considered and appropriately investigated.

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