Lessons to be learned: a case study approach

Primary hyperparathyroidism simulating an acute severe polyneuritis

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Abstract

The case is presented of a 65 year old lady with recent onset of neuromuscular manifestations, comprising paraparesis, areflexia and unsteady gait, along with episodes of slurring of speech and diplopia, later confirmed to be due to severe hypercalcaemia - which itself was caused by primary hyperparathyroidism. Restoration of normocalcaemia, by means of rehydration and bisphosphonate therapy, resulted in clinical improvement - whilst subsequent parathyroidectomy was followed by complete resolution of all symptoms. In order to make prompt differentiation between the neurological sequelae of hyperparathyroidism and a primary neurological disorder, a high index of suspicion is required. An urgent serum calcium assay, as part of a bone profile, is mandatory in patients who present with neurological symptoms - especially the elderly, amongst whom hyperparathyroidism is especially common.

Case History

A 65-year old lady was referred late one night by her general practitioner to the Accident and Emergency Department of the local hospital. There was a history of progressive weakness in both lower limbs over the previous seven days. She had been unsteady on her feet, had noted difficulty getting up and down the stairs and, in consequence, had sustained several falls - but, fortunately, without any serious injury resulting. There had been three brief episodes of slurring of speech three days before presentation; in addition, there had been diplopia over the last 24 hours. All these symptoms were preceded one week earlier by an episode of upper respiratory tract infection which had responded to a course of antibiotic therapy. The past medical history included hypertension of six years duration, long-standing migraine, appendicectomy and a hysterectomy operation for menorrhagia. Her current medications were Tenoretic (containing atenolol and chlorthalidone) for hypertension and Sanomigran (pizotifen - as hydrogen malate) for migraine. She was a non-smoker and did not take alcohol.

On physical examination she was overweight (body weight: 95 kg) and looked depressed - but was well orientated. The pulse rate was regular at 62 beats per minute and the supine blood pressure was 144/95 mm Hg; there was no postural fall. Apart from mild non-pitting ankle oedema, the significant findings were neurological. She was noted to be very unsteady on standing, with a tendency to fall backwards, had a shuffling gait and required support when walking. Both lower limbs were weak (more so proximally than distally) and areflexic; she had diminished perception of vibration, but there was no sensory loss. Examination of the upper limbs revealed them to be essentially normal, as also were the cranial nerves and fundi. Following a more formal neurological assessment, shortly after the initial general examination, a provisional diagnosis of probable Guillain-Barré syndrome was made.

Laboratory investigations on admission included urgent serum electrolytes and a renal profile, which revealed moderate hypokalaemia [serum potassium was 3.0 mmol/L (RR: 3.5-5.0)] and some impairment of renal function [serum urea was 9.3

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mmol/L (RR: 2.5-7.5) and the serum creatinine 152 umol/L (RR:60-120)]. A random plasma glucose was 5.9 mmol/L (RR: 3.0-5.0, fasting). Blood gas studies revealed the presence of a mild metabolic alkalosis. The full blood count, cerebrospinal fluid biochemistry and chest X-ray were all reported as normal. An electrocardiogram showed evidence of mild left ventricular hypertrophy. As part of the immediate management her antihypertensive therapy was changed from Tenoretic to atenolol, with oral potassium supplements in the form of Kloref. A five-day course of daily intravenous human normal immunoglobulin (Sandoglobulin) 30g was prescribed, assuming the diagnosis to be that of the Guillain-Barré syndrome; in addition, there were pulmonary function investigations in order to assess vital capacity - and studies to check nerve conduction.

The following morning, a full serum biochemistry profile was performed and this showed there was severe hypercalcaemia; the serum calcium was markedly elevated at 4.0 mmol/L (RR: 2.1-2.6) but the serum phosphate was low at 0.48 mmol/L (RR: 0.8-1.6). The serum albumin and alkaline phosphatase activity were both within their reference ranges, but the potassium level remained low at 3.0 mmol/L. These results led to revision of the diagnoses being considered, so that hypercalcaemia-related myopathy (possibly due to primary hyperparathyroidism) was included.

At this point the patient was commencing her first dose of Sandoglobulin; accordingly, this was stopped. Active rehydration was commenced with intravenous normal saline, to which was added potassium supplements. This produced a lowering of the serum calcium to 3.4 mmol/L and also improved renal function over the next 24 hours - after which followed an intravenous infusion of disodium pamidronate. Clinical examination and investigations showed no evidence of malignancy but further questioning unearthed the possibility of increased thirst and polyuria during the two weeks prior to admission. Serum protein electrophoresis was normal and a corresponding urine sample was negative for Bence Jones protein. The erythrocyte sedimentation rate (ESR) and thyroid function tests were normal. However, a serum intact parathyroid hormone (PTH) level was inappropriately elevated at 10.7 pmol/L (RR: 1.3-8.0). An ultrasound scan of the neck showed a right inferior lobe parathyroid adenoma, thus confirming a diagnosis of primary hyperparathyroidism. One week after admission her serum calcium had fallen and was stabilising at 2.37 mmol/L, serum phosphate was still low at 0.44 mmol/L but the renal function had by now become normal. She had by this time improved considerably clinically, with power returning to her limbs; she was successfully mobilised with the aid of a Zimmer frame. Intravenous fluids were stopped and oral fluid intake was encouraged. Two weeks after admission the serum calcium was 2.28 mmol/L; she could now walk unaided and was discharged home on amlodipine therapy for her hypertension.

The patient was re-admitted nine days later, this time electively, for surgical exploration of the neck. Preoperatively, the serum calcium was 2.36 mmol/L and the phosphate was 0.62 mmol/L. At operation a parathyroid adenoma was removed. The serum calcium and phosphate both returned to normal post-operatively. One and-a-half years after the operation the patient remained completely free of symptoms and the serum calcium was still normal.

Discussion

Primary hyperparathyroidism (PHPT) is the commonest cause of hypercalcaemia in the ambulatory population - and ranks second only to malignancy among hospitalised patients (Heath, 1991b). The condition most commonly occurs between the fourth and sixth decades of life and is three times more common in women than men, the female preponderance probably being entirely explained by the increased incidence after the menopause (Bhalla, 1986). The spectrum of possible presenting features in this disorder includes symptoms which may be non-specific, in addition to those which can be mild or severe; various clinical signs may also be present. (Table 1)

The availability of relatively simple, accurate and inexpensive automated methods for serum calcium measurement has permitted easy routine screening of patients in general; this has resulted in more cases of hypercalcaemia being identified - with the consequence of an apparent increase in the incidence of PHPT over that reported previously. It has also catalysed a change in the spectrum of clinical presentation of PHPT from that of renal stones, crippling bone disease and severe neuromuscular involvement to that of mild symptoms - or very often, no symptoms at all (Heath, 1991a; Trigonis et al, 1983; Turken et al, 1989). Consequently, the characteristics of the typical, modern day patient with PHPT are those of a female over 40 years of age (but, more often elderly) who has few or no symptoms clearly ascribable to a parathyroid disorder with, perhaps, some vague presentation such as depression or malaise - and with only modest elevation of serum calcium concentration (Heath, 1991b). The patient described here fits the description of the modern mode of presentation of hyperparathyroidism, except for the acuteness of onset of severe neuromuscular problems with severe hypercalcaemia.

Table 1

PRESENTING FEATURES OF HYPERCALCAEMIA

Non-specific symptoms
- Weakness
- Lethargy
- Depression

Mild Symptoms
- Dyspepsia
- Nausea
- Anorexia and vomiting
- Thirst and polyuria

Severe Symptoms and Signs
- Gross dehydration
- Renal colic
- Drowsiness
- Neuromuscular involvement
- Confusion and coma
- Cardiac arrhythmias

The diagnosis of PHPT was made in this case on establishing the same pattern in the serum bone profile as would normally be found in the uncomplicated situation, ie hypercal-

caemia (corrected for serum albumin), hypophosphataemia and the presence of an inappropriately high or normal concentration of intact PTH. The finding of a parathyroid adenoma on ultrasound scan further confirmed the diagnosis as correct - although in some cases the parathyroid pathology might even be missed. In all cases of hypercalcaemia, apart from PHPT, familial hypocalciuric hypercalcaemia and the rare ectopic PTH production, there should be suppression of plasma PTH; hence, a normal serum PTH - or a level above the reference range, in the presence of hypercalcaemia must, therefore, be deemed inappropriate. In the differential diagnosis of severe hypercalcaemia there are many clinical disorders to consider. (Table 2) Sometimes, serum phosphate concentration may be normal or even raised in PHPT; this occurs in circumstances where the hypercalcaemia has induced a significant degree of renal insufficiency - which, in turn, decreases phosphate excretion. Although this patient had some impairment of renal function, this was clearly not severe enough to mask the hypophosphataemia caused by PTH overactivity.

Table 2

CAUSES OF SEVERE HYPERCALCAEMIA
[serum calcium >3.0 mmol/L (RR: 2.1-2.6)]

Malignant disease
- Solid neoplasms
- Haematological

Hyperparathyroidism
- Primary
- Tertiary
- Multiple endocrine neoplasia

Non-malignant and non-parathyroid disorders
- Vitamin D excess
- Post-renal dialysis
- Milk alkali syndrome
- Idiopathic infantile hypercalcaemia

In this patient the severe neuromuscular involvement, with its rapidity of onset, bordered on what might be regarded as a hypercalcaemic crisis; indeed, the case was managed clinically as such. Generally, once the presence of severe hypercalcaemia has been established, the most important immediate consideration is to attempt to lower the serum calcium concentration to as normal a level as possible and to give any other supportive treatment depending on the overall symptomatology. The search for a definitive diagnosis should proceed concurrently, but not hamper the immediate management. In the context of hyperparathyroidism the results of serum PTH measurement are often not available in time to be of any practical help in the immediate management of the acute stage of the disorder. The clinical response of neuromuscular symptoms to treatment in this patient is consistent with the experience of others; in some cases symptoms were reversed by parathyroid surgery alone (Delbridge et al, 1988; Carnevale et al, 1992; Gentric et al, 1993) while, in another case, amelioration of symptoms was achieved by means of bisphosphonate therapy (Thomas and Lebrun, 1994). In this patient there was significant clinical improvement following restoration of normocalcaemia with rehydration and bisphosphonate therapy - and full recovery was achieved after the successful parathyroidectomy.

The neuromuscular complications of PHPT, first described in 1949 (Vicale, 1949) and reported also by others (Patten et al, 1974; Rollinson and Gilligan, 1977; Ljunghall et al, 1984; Delbridge et al, 1988; Carnevale et al, 1992; Gentric et al, 1993; Thomas and Lebrun, 1994) is now infrequently seen (Turken et al, 1989; Heath, 1991b). When present, the severity of symptoms is thought to relate to the chronicity of PHPT rather than to the absolute serum calcium level (Bhalla, 1986). In this particular patient, the exact timing of onset of the hyperparathyroid state is not known, but scrutiny of her past records revealed a normal serum calcium, bone profile and renal function three years prior to presentation.

The presentation in this case mimicked acute polyneuritis - and she commenced receiving the appropriate treatment for such, before a serum calcium result was available and the correct diagnosis of PHPT was even considered. Although the treatment initially received in this instance, ie intravenous human immunoglobulin, is generally safe it is not without potential, although uncommon, side-effects (Hughes, 1996). The pathogenic mechanism for neuromuscular involvement in PHPT remains ill-defined, but there is a suggestion that it may be a primary neuronal disorder, with impairment of neuromuscular transmission and secondary muscular involvement (Kaplan et al, 1982; Turken et al, 1989). The contribution to the degree of severity of symptoms by the mild hypokalaemia observed in this patient should at the most be only modest. Hypokalaemia is present in approximately five per cent of cases of PHPT (Stewart and Broadus, 1987) when it is probably a result of renal tubular acidosis induced by the hypercalcaemia or secondary hyperaldosteronism consequent upon intravascular volume contraction. Perhaps an additional factor in this patient was the thiazide component of her antihypertensive medication; this drug has the tendency not only to promote renal potassium excretion but also to perpetuate hypercalcaemia by enhancing renal calcium reabsorption.

Conclusions

It should be remembered that primary hyperparathyroidism remains a possible cause of severe neuromuscular disorder, in spite of the fact that the majority of patients with hypercalcaemia are now either asymptomatic or have only the mildest of symptoms. Such neuromuscular involvement may mimic a primary neurological disorder and an urgent bone profile (or, at least a serum calcium and albumin measurement) should help resolve the diagnosis at an early stage. Furthermore, the neuromuscular manifestations of hyperparathyroidism are eminently reversible by means of conservative management and/or surgery.

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EATING MATTERS: A Resource for Improving Dietary Care in Acute Hospitals

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