Learning from errors

The lady with a calcified brain

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Summary

The authors present here a case that demonstrates the importance of exclusion of metabolic conditions before giving a diagnosis of Fahr disease. This case also highlights the possibility of exacerbation of hypocalcaemia by antiepileptic agents.

BACKGROUND

Parathyroid hormone (PTH) regulates serum calcium concentration, which in turn regulates PTH secretion. Chronic hypoparathyroidism causes hypocalcaemia gradually, and is known to be associated with a wide repertoire of neurological symptoms and central nervous system calcifications. In this report, we describe a patient with neurological manifestations of primary hypoparathyroidism, which was likely complicated by chronic renal disease, vitamin D deficiency and metabolic consequences of antiepileptic medication use.

CASE PRESENTATION

A 48-year-old female was brought to our hospital with a history of seizures, abnormal gait and speech, behavioral dysfunction, cognitive decline and inability to attend to her activities of daily living. Seizures were first noted approximately 8 years before presentation. She had been managed with carbamazepine (maximum dose 800 mg/day), which was later changed to sodium valproate (maximum dose 800 mg/day). Treatment had been irregular, and seizures occurred at a frequency of one every 4 months; this had increased to one every week since 6 months. The last episode was 4 days before presentation. Over the preceding 6 months, she developed abnormal gait, accompanied by frequent falls and slurring of speech. Relatives noted forgetfulness, confusion and frequent inability to identify close family members. She was bed-bound since 2 months, with history of occasional urinary and bowel incontinence. No history of myoclonic jerks, hallucinations, weight loss, wasting or gastro-intestinal complaints was forthcoming. She had been diagnosed hypertensive several months ago, but was not taking any antihypertensive medications. She had never undergone any surgical procedures, and did not have history of thyroid disease. Family history was significant for hypertension alone. The patient had been referred to us following a CT brain.

On examination, pulse rate was 72/min, regular; blood pressure was 160/70 mm Hg and respiratory rate 15/min. Skeletal and skin examination did not reveal any abnormalities. Bilateral cataracts were noted. Trousseau's sign and Chvostek's sign were positive. The chest, cardiovascular system and the abdomen were normal. She was partially oriented to place, disoriented to time and could identify

a few of accompanying family members. Comprehension was limited to simple, single step commands. Spontaneous speech was monotonous, hypophonic and severely dysarthric. Cranial nerve examination was normal, without evidence of papilloedema. Gaze evoked nystagmus and dysmetric eye movements were evident. Bilateral horizontal gaze limitation was seen, with preservation of vertical eye movements. Tone was increased in all limbs, with predominance of rigidity. Power was greater than grade 4/5 in all limbs, deep tendon reflexes were exaggerated and plantars were bilateral extensor. Sensory examination showed preserved sensation of pain bilaterally. Severe truncal and appendicular ataxia was evident. Mask like facies, impaired postural reflexes and hypokinesia were noted, with occasional dystonic posturing of right-sided limbs.

Baseline investigations are as tabulated (table 1). ECG showed prolongation of the corrected QT interval (0.52 s). CT of the brain showed extensive, symmetric calcifications in the basal ganglia, cerebral subcortical areas and the cerebellum (dentate) (figures 1 and 2). Samples for serum PTH and vitamin D level were drawn before initiating treatment, and showed markedly low PTH level, with low serum vitamin D (table 1). Bone survey showed mild calcification of the interosseus membrane of the right

Table 1 Baseline investigations

Laboratory parameter	Value (normal)
Haemoglobin	10.2 g/dl
Total leucocyte count	11.0×10 ³ /microlitre
Platelets	362×10 ³ /microlitre
Blood urea	41 mg/dl
Serum creatinine	2.8 mg/dl
Serum sodium/potassium	143/3.3 mmol/l
Serum calcium	3 mg/dl
Serum phosphorus	6.4 mg/dl
Serum magnesium	1 mg/dl
Urinary calcium (24 h)	1.9 mg/24 h
Ultrasound KUB	Grade II medical renal disease
Serum albumin	3.6 g/dl
Urine routine	Proteins +
Serum parathyroid hormone (intact)	1 pg/ml (15–68)
Serum vitamin D (1,25 dihydroxy)	29.3 pmol/l (39–193)
Thyroid stimulating hormone	0.67 uIU/ml (0.3–5)

KUB, kidney, urinary tract and bladder.

Figure 1 CT image showing intracranial calcification.

forearm. Ultrasound of the abdomen showed evidence of medical renal disease (grade II), without evidence of nephrolithiasis.

Based on clinical and laboratory evidence, the patient was diagnosed as primary hypoparathyroidism.

TREATMENT

Treatment was initiated with intravenous calcium and magnesium, initially, along with intramuscular Vitamin D. Antiepileptic treatment was modified as per body weight, though the antiepileptic drugs (AED) (carbamazepine) was not changed.

OUTCOME AND FOLLOW-UP

After 24 h, improvement was noted in the neurological status. Orientation to person and time improved, and she was able to identify family members. Responses were relevant, and an improvement in balance was evident. She was discharged on oral calcium and vitamin D3 supplements. Gradual improvement in serum calcium, magnesium levels was concurrent with improvement in gait and performance of ADLs. On follow-up 1 month later, she was ambulant independently, significant improvement was noted in the cerebellar and extrapyramidal functions, and there had been no seizure recurrence.

DISCUSSION

The observation of an inappropriately normal PTH in a patient with hypocalcaemia warrants the diagnosis of hypoparathyroidism. Hypoparathyroidism is known to be

Figure 2 Intracranial calcification.

associated with several neurological presentations, the most common being seizures and mental changes.¹ Movement disorders, including parkinsonian features, chorea and dystonia have been frequently reported, while cerebellar dysfunction is not common.² The mechanism of extrapyramidal and cerebellar signs is unclear, and severity is not proportional to the extent of cerebral calcification.^{3 4} The cause of cerebral calcification itself is not yet known, and may be connected to chronic elevation of serum phosphate.^{1 5}

The biochemical status in untreated hypoparathyroidism includes low or absent serum PTH levels, hypocalcaemia, high urinary calcium excretion (hypercalciuria), hyperphosphatemia and reduced levels of 1,25-dihydroxyvitamin D.^{6 7} In our patient, low PTH level was seen in conjunction with low vitamin D level and hypocalciuria, suggesting a co-occurrence of primary hypoparathyroidism with Vitamin D deficiency. Though low dietary intake could be responsible for the vitamin deficiency, laboratory evidence indicated presence of chronic renal disease (likely related to untreated hypertension) which may have contributed to a vitamin D deficient state in our patient. There is evidence linking metabolic abnormalities, including hypocalcaemia and reduced vitamin D levels, to the use of AEDs.^{8 9} Our patient had been taking sodium valproate and/or carbamazepine for several years; it is possible that the AEDs may have led to worsening of the underlying metabolic abnormalities.

The current treatment of hypoparathyroidism consists of calcium and vitamin D supplementation; lately, subcutaneous administration of intact PTH has been reported to be

safe and effective.¹⁰ Correction in calcium level is known to improve the neurological status, as was clearly evident in our patient.¹⁻⁴ Occasionally, large amount of supplemental calcium (3–4 g/day in our patient) and vitamin D may be essential for correction of calcium levels. This carries an inherent risk of hypercalciuria, nephrolithiasis and vitamin D toxicity. Regular monitoring of serum calcium levels and urinary calcium excretion, are thus essential in such patients.

Cerebral calcifications are a hallmark of Fahr disease, which is a rare, idiopathic, neurodegenerative disorder, that is often familial. The calcification in Fahr disease is characterised by bilateral basal ganglia calcification, the commonest site being the globus pallidus. However, the disease is idiopathic and the laboratory parameters in patients with Fahr disease reveal normal calcium, phosphorus and PTH levels. There is neither a cure, nor a standard course of treatment for Fahr disease. The gratifying response to treatment in our patient underlines the importance of identifying metabolic abnormalities in patients who would otherwise be diagnosed as Fahr disease.

Learning points

- Long-term antiepileptic use can aggravate manifestations of hypoparathyroidism by increasing degree of hypocalcaemia.
- Other causes of intracranial calcification should be ruled out before labelling a case as Fahr syndrome.

Competing interests None.

Patient consent Obtained.

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