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BRIEF REPORT

Posterior reversible encephalopathy syndrome and parkinsonism as the first manifestation of primary hyperparathyroidism - a report of two cases

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Abstract

Background/objective Primary hyperparathyroidism (PHPT) may be asymptomatic or present with renal calculi, secondary osteoporosis, fractures and neuropsychiatric manifestations. Posterior reversible encephalopathy syndrome (PRES) and parkinsonism are atypical manifestations that may be rarely associated with PHPT. We report two patients who presented with the conditions mentioned above.

Case report The first patient involved a 38-year-old woman who presented with diminution of vision, seizures, altered behavior and hypertension over eight months. An MRI of the brain done had shown vasogenic edema involving the parieto-occipital regions, suggestive of PRES. A metabolic screen revealed PTH-dependent hypercalcemia that was localized to the left inferior parathyroid gland. Following focused parathyroidectomy, there was improvement in sensorium, vision and normalization of blood pressure. The second patient was of a 74-year-old man who presented with progressive extra-pyramidal symptoms of gait abnormalities and rigidity since the past eight months. He was initiated on Selegeline and Levodopa for the same purpose, and subsequently reported minimal improvement in symptoms. Investigations revealed PHPT associated with a right inferior parathyroid adenoma. Within two weeks following surgery, there was an improvement in rigidity and gait and he was able to ambulate without support.

Discussion PRES has been reported to occur in the context of preeclampsia, hypertension, infection, sepsis and autoimmune conditions. PRES associated with hypercalcemia is rarely reported. While extra-pyramidally related manifestations are described in hypoparathyroidism, PHPT related parkinsonism is not commonly encountered. Identifying the underlying aetiology and initiation of corrective measures may lead to amelioration of patient symptomatology.

Conclusion The occurrence of PRES and parkinsonism is rare in primary hyperparathyroidism; the two patients described above highlight the importance of screening for hypercalcemia in the setting of neurological manifestations.

Keywords Primary hyperparathyroidism · Hypercalcemia · Posterior reversible encephalopathy syndrome · Parkinsonism

Introduction

Primary hyperparathyroidism (PHPT) may present with various neuropsychiatric manifestations that range from "fatigue overtones" to impaired concentration, altered mental status, confusion, irritability and hypercalcemia related encephalopathy [1, 2]. PHPT, may occasionally present with atypical neurological manifestations which include posterior reversible encephalopathy syndrome (PRES), parkinsonism and paraparesis; it may also mimic neurodegenerative conditions such as motor neuron disease (MND) and multiple sclerosis. A knowledge of these disorders is needed, as all the aforementioned debilitating neurological manifestations may be potentially reversible on treating the underlying PHPT with urgency. In this report, we describe two patients with primary hyperparathyroidism, who presented with atypical neurological features which included PRES and parkinsonism.

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Case 1

A 38-year-old woman, presented with acute onset loss of vision with altered sensorium loss 8 months ago, recurrent seizures with altered behavior for 2 months. Eight months ago, she underwent cholecystectomy for abdominal pain with vomiting. She had deranged liver function tests and was with cholecystitis. Surgery was uneventful, however, on fifth post-operative she developed acute painless loss of vision involving both eyes followed by alteration of sensorium. She had no seizures, focal motor or sensory deficits. Blood pressure recording were noted to be high and was managed as hypertensive emergency. She was managed in intensive care unit and she was noted to have gradual improvement of sensorium with preserved language, memory, motor and sensory findings. However she was noted to have nil perception to light in both eyes and was discharged with grave prognosis in recovery of vision. She was able manage daily activities with support, due to persistent visual impairment. For last 4 months, she was noted to have gradual decreased hearing in both ears with no pain, tinnitus or discharge. There was also decreased perception of touch and pain over distal extremities in upper and lower limbs with no motor deficit. She developed recurrent generalized tonic-clonic seizures with post-ictal confusion, altered behavior with fluctuating sensorium for last 2 months. There was no associated fever, headache, vomiting, bladder or bowel disturbance. She presented to our center for further evaluation.

At presentation, she was drowsy but arousable, with prolonged response time. Her Glasgow Coma Scale (GCS) score was 10/15 (E2V3M5); blood pressure (BP) was 180/120 mm Hg and she was euvolemic. Speech was incomprehensible words and she was unable to comprehend or follow simple commands. Menace reflex was negative indicating visual impairment. Pupils were 2.5 mm and reactive to light. Fundus examination was normal. There was facial asymmetry of gross motor deficits of any limbs. She had no neck stiffness. Neck examination revealed a palpable nodule 2*1 cm inferior to the left lobe of the thyroid.

The possible etiologies considered were vascular (posterior circulation stroke, posterior reversible encephalopathy syndrome), infective (prion disease - variant CJD / Subacute sclerosing panencephalitis), paraneoplastic, metabolic, toxic and mitochondrial related disease. An MRI of the brain revealed bilaterally symmetrical vasogenic oedema involving both parieto-occipital regions and the splenium of the corpus callosum that was suggestive of atypical posterior reversible encephalopathy syndrome (PRES) along with cerebral volume loss that was disproportionate for her age (Fig. 1). An Electroencephalogram (EEG) showed demonstrated posterior hemispheric epileptiform activity. CSF studies were normal. The exact aetiology of her hearing loss could not be ascertained. There was no evidence of any ear pathology and clinical examination showed the tympanic membrane on both sides to be intact. Her autoimmune and vasculitic work up were negative. Syphilis screen was negative. Moreover, PCR for multiple viruses were done that included herpes simplex 1 and 2, cytomegalovirus, adenovirus, Ebstein Barr virus and these were negative. Measles screen also was negative.

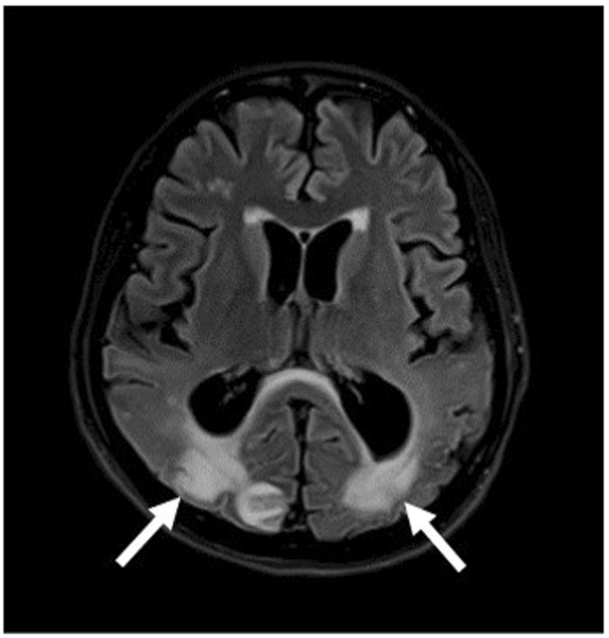

Fig. 1 MRI Brain - FLAIR images showing vasogenic edema in the parieto-occipital regions

She was noted to have a parathyroid hormone (PTH) dependent hypercalcemia with the highest albumin corrected calcium being 12.8 mg/dL (N: 8.3–10.4 mg/dL) and PTH of 434.1 pg/mL (N: 8–80 pg/mL). There was no family history to suggest syndromic associations of familial PHPT or multiple endocrine neoplasia. The patient had no prior history of fractures or renal calculi or dyspeptic symptoms. Serum prolactin was 13.8 ng/mL (N: 2.8–29.2 ng/mL). In view of her initial high blood pressure a work-up for phaeochromocytoma was done and it was ruled out. The 24-h urine metanephrine and normetanephrine were 135 mcg ($N < 350$ mcg) and 241 mcg ($N < 600$ mcg) respectively. The serum creatinine was 0.96 mg/dL, fasting phosphate was 1.6 mg/dL and the 24-h urine calcium and creatinine were 571 mg (11.4 mg/kg/day; N: < 4 mg/kg/day) and 594 mg respectively (Urine volume was 3760 mL). The calcium-creatinine ratio was 0.07 and TmP/GFR was 1.7 (N: 2.5–4.5). Serum alkaline phosphatase was 164 U/L (N: 40–125 U/L) and 25 (OH) vitamin D was 17.9 ng/mL (N: 30–75 ng/mL). Other serum electrolytes were normal. A detailed skeletal survey was not done because of her fluctuating sensorium and altered behavior. However, a DXA was done which showed low bone mass at all three sites.

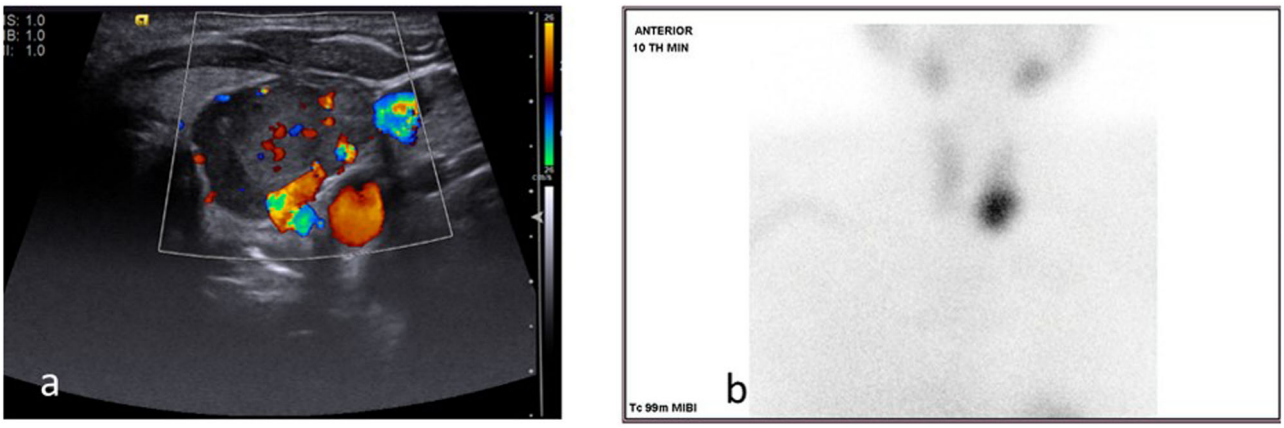

Fig. 2 **a** USG neck showing well defined hypoechoic lesion with increased vascularity and possible polar artery, in subcapsular location along the inferior pole of the left thyroid lobe. **b** Sestamibi scan showing increased tracer accumulation in left inferior parathyroid gland

Neck of Femur (NOF): BMD: 0.522 g/cm^2 T-score: −2.9, Z-score: −2.7

Lumbar Spine (L1–L4): BMD: 0.606 g/cm^2 T-score: −4.0, Z-score: −3.9

Distal 1/3 of radius: BMD: 0.448 g/cm^2 T-score: −4.1, Z-score: −3.8

Further localization studies for primary hyperparathyroidism showed a left inferior parathyroid adenoma on an ultrasonogram (USG) of the neck and a sestamibi scan (Fig. 2a, b). USG of the abdomen showed a 13 mm calculus in right vesico-ureteric junction with ipsilateral moderate hydroureteronephrosis.

She was initially managed with hydration with subsequent decrease in calcium levels to 10.9 mg/dL. The blood pressure was controlled with amlodipine 5 mg once a day and she was started on oral anti-epileptic medications. She underwent left inferior parathyroidectomy and the histopathology of the resected tumor was consistent with that of a parathyroid adenoma with no morphological features of a malignancy. Postoperatively, the calcium levels normalized and there was gradual improvement in sensorium. There was no post-op hypocalcaemia. Albumin adjusted calcium in the post-op period was 9.1 mg/dL and the PTH had decreased to 41.2 pg/mL. She was alert, oriented, comprehending speech, following commands and fluency improved. Her vision, which was nil perception to light in both eyes, improved to identifying direction of projection of light and perceiving hand motion at 1 m. Visual evoked potential to pattern reversal stimulus showed normal waveform with normal latency of 95 ms. During her course of stay she noted improvement in sensations of extremities and was able to track objects in her visual field at 3 m distance. Blood pressure normalized, there was no further seizures, anti-hypertensives and anti-epileptic medications were gradually tapered and stopped. At follow-up, her vision in the right eye was 6/24 and in the left eye was 6/18 after six months. At 18 months follow-up, visual acuity was reported to be 6/18 in both eyes. Moreover, her audiogram was reported as a moderate to profound sensori-neural hearing loss. There was no evidence of any ear pathology and on clinical examination the tympanic membrane on both sides were normal. She was advised a trial of hearing aid as she could understand and interpret some spoken commands.

Case 2

A 74-year-old man presented with progressive slowing of gait, difficulty in rising from a squat and frequent fall over an 8-month duration. Pre-morbidly, he was independent in his activities of daily living and did not have memory, cognitive or behavioral abnormalities. He had slowness of gait with stooping posture and frequent forward falls. His gait progressively worsened over time, requiring support to walk, and was confined to bed for last 2 months, dependant on caregivers for activities of daily living. One month prior to presentation at our center, he developed progressive deterioration in his sensorium. On clinical examination, he had fluctuating sensorium with best GCS score of 14/15 (E3V5M6). He was dehydrated with blood pressure of 110/70 mm Hg. Cranial nerve examination was normal, with normal eye movements. There was cog wheeling rigidity of limbs with bradykinesia and no tremors, no motor and sensory deficits, and no neck stiffness.

A provisional diagnosis of progressive extrapyramidal syndrome (EPS) was made, and he had only minimal improvement with Levodopa and Selegeline which was started at hometown. The patient had not received any drugs which would cause drug induced parkinsonism such as Domperidone, Metoclopramide, Levosulipirde, antipsychotic agents. A plain CT had been done at admission which ruled out intra-cranial calcification. Investigations revealed the serum calcium to be 15 mg/dL with a PTH of 236 pg/mL and

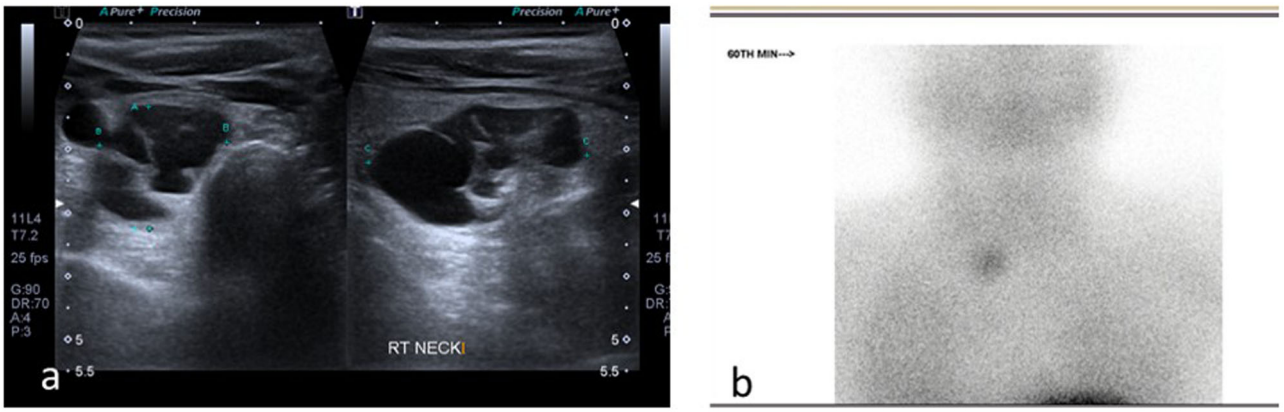

Fig. 3 **a** USG neck showing large lobulated exophytic solid cystic lesion from lower pole of right lobe of thyroid gland. **b** Sestamibi scan showing increased tracer uptake in right inferior parathyroid gland

fasting phosphate of 2.4 mg/dL. The hypercalcemia may have unmasked or worsened an underlying Parkinson's disease in this patient. Serum creatinine was 1.84 mg/dL with an estimated glomerular filtration rate (eGFR) was 32 mL/min/1.73 m2. Serum sodium was 141 mmol/L (N: 136–145 mmol/L). He was started on oral and intravenous fluids. He received a bolus of one litre of normal saline followed by 150 mL per hour for about 18 h. As hypercalcemia remained refractory to conservative measures, he was administered one dose of denosumab 60 mg s/c as well as one session of hemodialysis. The calcium/creatinine clearance could not be done as the patient was sick at admission; he was administered denosumab which could alter the 24-h urine calcium; hence this was not done. Following dialysis, he was started on oral cinacalcet 30 mg once daily. There was gradual improvement in his sensorium and he was able to communicate well as his calcium levels normalized. As he continued to have clinical features of rigidity and required support to ambulate, he was continued on his anti-parkinsonian medication. Sonogram of the abdomen had shown sub-centimetric renal calculi and these were managed conservatively. Bone densitometry revealed osteoporosis as follows:

NOF: BMD: 0.472 g/cm^2 T-score: −3.4, Z-score: −2.0

L1-L4: BMD: 646 g/cm^2 T-score: −4.0, Z-score: −3.0

Distal 1/3 of radius: BMD: 0.625 g/cm^2 T-score: −3.6, Z-score: −2.0

There was no history of prior fractures. There was no significant family history of similar complaints or syndromic associations. Localization studies for primary hyperparathyroidism revealed a right inferior parathyroid adenoma (Fig. 3a, b). He underwent focused parathyroidectomy of right inferior parathyroid lesion, the histopathology of which was reported as an atypical parathyroid adenoma with no definite features of malignancy. Following surgery he was cured of hypercalcemia; he required parenteral calcium infusion, oral calcium supplements as well as calcitriol as he had developed hungry-bone syndrome. Following surgery, he was able to walk without support at the time of discharge with significant improvement in rigidity. His speech had also improved. At admission, he had been on Tab. Syndopa 125 mg 4 times daily and Tab. Selegiline 5 mg twice daily for the previous 3 months with progressive worsening of rigidity. At the time of discharge, his medications were reduced to Tab. Syndopa 125 mg half tablet thrice daily; Tab. Selegeline was stopped. On follow-up after four months, he was completely independent in his activities of daily living.

The laboratory parameters of both patients are shown in Table 1.

Discussion

Here, we report two patients who had presented with atypical neurological manifestations namely posterior reversible encephalopathy syndrome and parkinsonism. The occurrence of these is extremely rare in primary hyperparathyroidism; the above two cases highlight the importance of screening for hypercalcemia in the setting of neurological manifestations.

Posterior reversible encephalopathy syndrome (PRES) is a reversible encephalopathy characterized by subcortical vasogenic oedema predominantly involving the parieto-occipital lobes. Patients with PRES present with acute neurological manifestations that include seizures, cortical blindness, altered sensorium, headache, and rarely focal neurological deficits [3]. Usually, all the features though clinically severe and acute, are completely reversible on timely recognition of condition and treatment of the underlying cause. PRES has characteristic MRI findings of hyperintensities on T2 and FLAIR sequences predominantly seen in the posterior circulation. The pathophysiology of PRES involves the breakdown of the blood-brain barrier due to sudden changes in blood pressure (BP) or direct toxic effects on the endothelium, resulting in brain

Table 1 Laboratory parameters of Case 1 and Case 2

Lab parameter Normal range, units	Case 1 (baseline)	Case 1 (post-op)	Case 1 (18 months)	Case 2 (baseline)	Case 2 (post-op)
Calcium 8.3–10.4 mg/dL	12.8	9.1	9.6	15	8.6
Phosphate 2.5–4.5 mg/dL	1.6	2.2	4.1	3.6	3.8
25 (OH) vitamin D 30–75 ng/mL	17.9		27	32.5	
Parathormone 8–80 pg/mL	434.1	41.2	44	236	7.2
Creatinine 0.7–1.2 mg/dL	0.96		1.0	1.84	1.01
Alkaline phosphatase 40–125 U/L	164		58	105	

edema [3]. The preferential involvement of the posterior regions of brain in PRES is explained by the relatively sparse sympathetic innervation of the vertebrobasilar system, a factor that maintains cerebrovascular autoregulation by compensatory vasodilation during cerebral hyperperfusion, thereby protecting the brain from damage due to severe hypertension [4, 5]. The major causes include pre-eclampsia/ eclampsia, allogenic bone marrow transplantation, cytotoxic drugs, solid organ transplantation, and autoimmune disorders [6]. Hypercalcemia is a rare cause of PRES reported mainly in patients with severe hypercalcemia, secondary to malignancy [7], iatrogenic causes [8], vitamin D toxicity [9], or granulomatous etiology [10]. Primary hyperparathyroidism (PHPT) as a cause of PRES is rarely reported with only few cases in world literature [11–16]. There have been multiple mechanisms proposed for hypercalcemia-induced PRES as follows:

a. Cerebral vasospasm [17, 18]: Hypercalcemia leads to augmented actin-myosin coupling causing vascular smooth muscle contraction with cerebral vasospasm and consequent endothelial cell injury and PRES.
b. Hypertension [19]: Acute hypercalcemia causing hypercatecholaminemia with sudden rise in blood pressure leading to PRES.
c. Direct effects [20, 21]: Hypercalcemia by increasing expression of nitric oxide synthase, endothelin-1, and pro-inflammatory cytokines leads to endothelial dysfunction and PRES.
d. Hypomagnesemia: [7] Hypercalcemia causing hypomagnesemia with failure of cerebral autoregulation and subsequent PRES.

The rarity of this association can be explained based on the facts that most patients with PRES do not have calcium levels evaluated and hypercalcemia presenting with altered sensorium do not undergo neuro-imaging, thereby missing a diagnosis of PRES.

While hypoparathyroidism is known to manifest with extra-pyramidal features due to calcification of the basal ganglia, parkinsonism is rarely reported with primary hyperparathyroidism. Augusto CMG reported a 75-year-old woman who presented with a hypercalcaemia related to primary hyperparathyroidism. She developed symptoms of parkinsonism; following parathyroid surgery, the parkinsonian features improved and she was asymptomatic at three years of follow-up [22]. Luján-Martínez D et al. reported significant improvement in symptoms of parkinsonism following excision of a parathyroid adenoma in a 70-year-old woman [23]. Furthermore, there was spontaneous resolution of parkinsonism in a patient after parathyroid surgery as reported by Kovacs et al. [24]. Ohya Y on the other hand described an 83-year-old lady with a right thalamic bleed and a drug-induced parkinsonism who presented with worsening symptoms of parkinsonism. She was detected to have a PTH-dependent hypercalcaemia. The features of parkinsonism were resistant to the addition of other anti-Parkinson's medications. With the initiation of cinacalcet, there was normalization of PTH and calcium and improvement in the patient's symptoms [25].

Due to the paucity of cases of primary hyperparathyroidism presenting with features of parkinsonism, the exact mechanism for this association remains speculative. It is known that Parkinson's disease results from a decrease in the dopaminergic transmission in the nigrostriatal pathway. Calcium is required for neuro-muscular stimulation as well as neuro-muscular transmission. Hypercalcemia is reported to result in large quantities of dopamine being secreted into the synaptic cleft leading to a down regulation of dopamine receptors. Moreover, the elevated levels of iPTH is also reported to cause neurotoxicity and apoptosis independent of hypercalcemia. Hypercalcemia may also be responsible for aggravating levodopa resistant parkinsonism [22].

The abovementioned individuals presented predominantly with neurological symptoms and were diagnosed to have posterior reversible encephalopathy syndrome and parkinsonism respectively. Incidentally they were detected to have hypercalcemia secondary to a primary hyperparathyroidism. Both patients made significant improvement upon addressing the primary metabolic insult.

Conclusion

Beyond the usual neuropsychiatric disturbances, primary hyperparathyroidism may present with rare and atypical

neurological manifestations. Posterior reversible encephalopathy syndrome and parkinsonism are exceptional and infrequent associations. This calls for treating physicians to take cognizance of these rare manifestations of primary hyperparathyroidism as timely detection and initiation of appropriate therapeutic measures will help in reducing the morbidity associated with them.

Author contributions SSR and MAH wrote the manuscript MR, GAN, AVN, DB helped in data curation KEC, ATP, TVP and NT reviewed the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical disclosure Informed consent was taken from the patient. The authors declare that no patient data appears in the article.

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