Intracerebral Calcification, Seizures and Hypocalcaemia: A Tale of Two Bahraini Patients

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Abstract: The combination of hypocalcaemia, seizures or extrapyramidal symptoms should alert the treating physician to assess for intracerebral calcification(ICC) on brain computerized scan (CT). Should the ICC be shown then the likely diagnosis is hypoparathyroidism. We describe two cases of idiopathic hypoparathyroidism who presented with hypocalcaemia, neurological diseases and ICC. The Authors present the clinical and radiological findings and review this rare presentation of a rare disease. **Summary:** The first patient was a 40 -years old Bahraini female, have been observed to have hypocalcaemia three years earlier, who presented with seizures. The second patient was a 20-years old Bahraini male who was referred for the management of poorly controlled Epilepsy associated with the diagnosis of juvenile Parkinson's 8 years earlier. **Background:** Hypoparathyroidism can present with neurological symptoms like seizures, paresthesia, depression, psychosis, extrapyramidal manifestations and features of raised intracranial pressure. Hypoparathyroidism and pseudohypoparathyroidism are the most common causes of pathological Intracerebral Calcification. The standard therapy is calcium and vitamin D replacement although there is recent evidence that PTH replacement may play a role. The cases illustrate the delay in diagnosis of both cases and are presented to increase awareness of hypoparathyroidisms and its long term neurological complications which are related to uncontrolled chronic hypocalcaemia and hyperphosphatemia.
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Keywords: Intracerebral Calcification, Basal Ganglia calcification, Hypoparathyroidism.

Cases presentation:

Case 1.

A 40 years old Bahraini Female was brought by the ambulance after a seizure at a shopping mall. She had recurrent fainting attacks for which she had sought medical advice only once but was not investigated and was not on any treatment. She had been told to have low calcium during her pregnancy three years prior to her current presentation and was on calcium supplements. On arrival to the emergency department she was conscious and oriented and had normal neurological and cardiac examination. The ophthalmology review demonstrated posterior sub capsular cataract and cortical cataract LE.

Her laboratory investigations showed the following: Calcium 1.24 mmol/L(ref range 2.2-2.55 mmol/L), ionized calcium 0.86 mmol/l(1.12-1.32), albumin 43.8 G/L (ref. range 35-50G/L), PO4 1.49 mmol/L (ref. range 0.87-1.45 mmol/l), Parathyroid hormone level 4.53 pg/L (ref range 16-65 pg/L), Mg 0.79 mmol/L(ref range 0.7-1.05 mmol/l), urea 4.2 mmol/L (ref. range 2.9-8.3 nmol/l), creatinine 65 Ummol/L (Ref range 45-84 Ummol/L), urinary calcium 0.89 mmol over 24 hrs in 1700 ml of urine (ref range 2.5-6 mmol/L), vit D 48 nmol/L (ref range 25-250 nmol/l). The Electrocardiograph showed a QT interval of 0.444 msec.

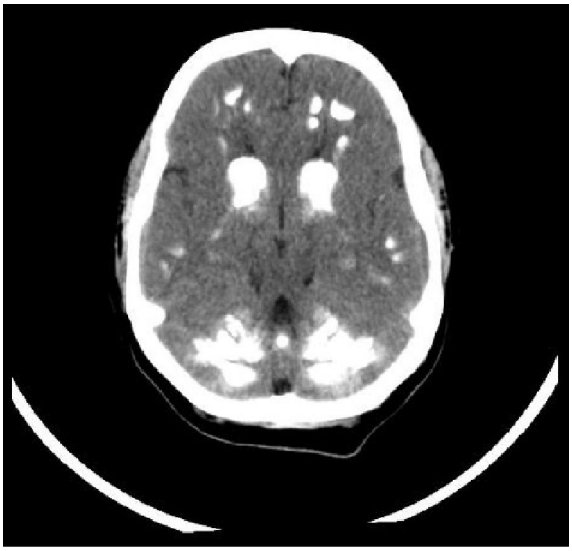
The seizure was attributed secondary to hypocalcaemia due to primary hypoparathyroidism. The non-contrast CT brain (Figure-1) showed bilateral extensive dense calcifications in the basal ganglia, thalami cerebrum and cerebellum. She was treated with Calcium gluconate 10% infusion and One alpha tablets. With the improvement in her calcium level she was switched to oral calcium carbonate and vitamin D3.

On discharge her calcium had reached 2.16 mmol/L and phosphate 1.97 mmol/L. She follows up in the endocrinology outpatient clinic.

Case- 2

A 20-year-old Bahraini male patient was referred to the neurology clinic for evaluation and the treatment of poorly controlled epilepsy. He was on Phenytoin 400 mg OD with frequent breakthrough seizures despite compliance and therapeutic phenytoin level. His diagnosis with epilepsy dated to year 2009 when he was thirteen-year-old. At the age of 15 years (in 2011) he was diagnosed with juvenile Parkinson disease and treated with L-dopa for few months. He had been treated before with valproate which was shifted to phenytoin in 2013. He remained on phenytoin until he was reviewed in the neurology clinic in August 2016. On further interrogation with the patient; his history was punctuated by frequent breakthrough seizures and occasional dystonic posturing of the left upper extremity. He did three MRIs and all reported as degenerative changes in the

basal ganglia. CT brain was not done before. His family history was negative for epilepsy, febrile convulsions or any movement disorder.

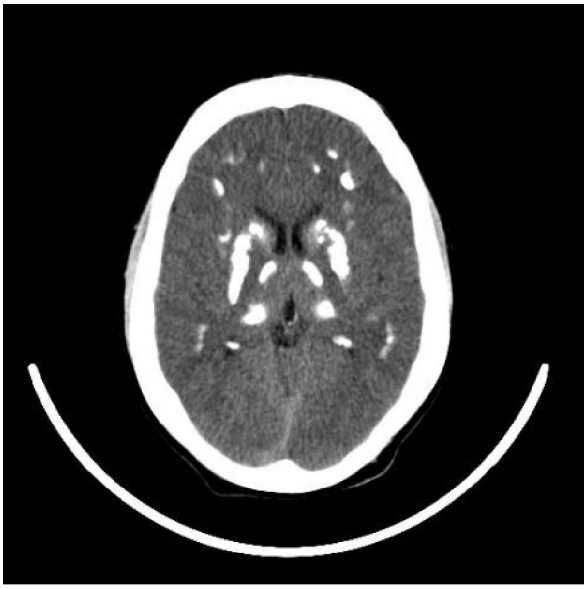


(Figure-1):
Non-contrast CT brain showed bilateral extensive dense calcifications in the basal ganglia, thalami cerebrum and cerebellum

On examination in the clinic he was conscious with frequent left hemi facial grimacing and head-jerking movement. The cranial nerves examination was normal. He had normal muscle tone, power, reflexes and coordination. The Chvostek sign was negative yet Trousseau sign was positive.

His laboratory investigations showed the following: Calcium 1.46mmol/L(ref range 2.2-2.5 mmol/L), albumin 43.9 G/L (ref. range 35-50G/L), PO4 2.34 mmol/L (ref. range 0.87-1.45 mmol/l), Parathyroid hormone level was 10.28 pg/L (ref range 1.6-6.9 pg/L), Mg 0.78 mmol/L (ref range 0.7-1.05 mmol/l), urea 5.4 mmol/L (ref. range 2.9-8.3 mmol/l), creatinine 69 Ummol/L (Ref range 59-104 Ummol/L), urinary calcium (not available), vit D 23.2 nmol/L (ref range 25-250 nmol/l). The Electrocardiograph was normal.

In view of his blood test a CT brain was ordered and showed Extensive symmetrical bilateral parenchymal calcifications, involving the basal ganglia, thalami, subcortical white matter and also the cerebellar hemispheres (Fig. 2). The patient was treated with calcium and vitamin D supplement and smoothly shifted to levetiracetam 1500 mg twice daily with control of his seizures.



(Figure-2):
Non-contrast CT brain showed Extensive symmetrical bilateral parenchymal calcifications, involving the basal ganglia, thalami, subcortical white matter and also the cerebellar hemispheres.

Discussion

Primary hypoparathyroidism is an uncommon condition in which your body secretes abnormally low levels of parathyroid hormone (PTH). PTH plays a key role in regulating and maintaining a balance of your body's levels of calcium and phosphorus. The low PTH in primary hypoparathyroidism leads to abnormally low ionized calcium levels in the blood and bones and an increase of serum phosphorus. (1) Mayoclinic.org.

Clinically, primary hypoparathyroidism manifests predominantly as neuromuscular dysfunction caused by hypocalcaemia. Intracranial calcification, in particular Basal ganglia calcification is associated with primary.

hypoparathyroidism.

Hypoparathyroidism can be due to acquired or hereditary causes. [1] Acquired hypoparathyroidism is usually due to removal of parathyroid gland during neck surgeries for thyroid and parathyroid glands. [1] Other rare causes of acquired hypoparathyroidism include radiation induced damage subsequent to radio iodine therapy, sarcoidosis, hemochromatosis, haemosiderosis, Wilson's disease and metastatic infiltration of parathyroid gland. [1,2] Hereditary hypoparathyroidism can occur as an isolated defect without other endocrine or dermatological manifestations (then it is referred to as idiopathic hypoparathyroidism) but more typically hereditary hypoparathyroidism occur along with other developmental anomalies such as defective

development of thymus or failure of adrenals, thyroid or ovaries along with mucocutaneous candidiasis, alopecia and vitiligo. [1] Idiopathic and hereditary forms of hypoparathyroidism usually manifest with in the first decade of life, although they can present later. [1]

The common clinical features of primary hypoparathyroidism are mainly due to hypocalcaemia and include circumoral numbness, paresthesia, spasms of carpal and pedal muscles, laryngeal spasm, tetany and seizures. [2] Important signs on physical examination include Chovstek's sign and Trousseau's sign. Neurological manifestations apart from seizures include raised intracranial tension, papilledema, irritability, depression, psychosis, extrapyramidal and cerebellar manifestations. [1,3–8] Other features include chronic changes in finger nails and hairs, extra osseous calcification and lenticular cataracts, heart failure and QT prolongation. [1]

Laboratory evaluation to diagnose primary hypoparathyroidism should include serum calcium (total as well as ionized), phosphorous, serum albumin, creatinine, magnesium, intact PTH and 25-hydroxyvitamin D levels. [2] Serum calcium levels are low, phosphate levels are high and intact PTH level are inappropriately low in hypoparathyroidism. Patients with pseudohypoparathyroidism also have low calcium, high phosphorus, but high PTH levels. [2] Measurement of 25-hydroxyvitamin D levels is important to rule out vitamin D deficiency as a cause of hypocalcaemia. Measurement of magnesium is also important as magnesium depletion or excess can also cause hypocalcaemia by inducing functional hypoparathyroidism. [12] Primary hypoparathyroidism was diagnosed in our patient on the basis of low serum calcium (ionized and total), high phosphate and very low PTH levels in face of normal Magnesium levels.

Electro encephalo gram (EEG) in the presence of hypocalcaemia can show evolution from alpha through theta and delta dominance, generalized spikes and sharp-waves burst of delta activity with sharp components. [13]

Radiological feature of primary hypoparathyroidism include **Intracerebral** calcification most commonly involving bilateral basal ganglia. [14] Calcification can also occur in cerebellum, sub cortical white matter, corona radiata and thalamus.

Intracerebral calcification can also be physiological in 0.3-1.5% of subjects. [15] Most common pathological causes of basal ganglia calcification are hypoparathyroidism and pseudohypoparathyroidism. Other causes of basal ganglia calcification are Fahr's syndrome, tuberous sclerosis, Cockayne's syndrome, and mitochondrial disease, and familial idiopathic basal ganglia calcification, diffuse neurofibrillary tangles with calcification, Down's syndrome and post infectious.

Treatment of primary hypoparathyroidism involves replacement with vitamin D or 1, 25 $(OH)_{2D3}$ (calcitriol) along with high dose of calcium. For most of the patients' vitamin D in a dose of 40,000-120,000 U/day (1-3 mg/day) with elemental calcium in a dose of ≥1 gm/day are usually satisfactory. [1] Oral calcium and vitamin D restore the overall calcium-phosphate balance but do not reverse hypercalcuria seen in hypoparathyroidism, therefore after vitamin D and calcium replacement excessive urinary calcium excretion can lead to kidney stone formation. Thiazides diuretics can lower urinary calcium excretion in such patients. [1]

Despite some uncertainty about the exact pathogenesis of ICC, treatment is known to prevent progression. Thus, clinicians are advised to:

1. Investigate for hypoparathyroidism in the presence of basal ganglia calcification.
2. Identify any manifestations of basal ganglia calcification and primary hypoparathyroidism, including cognitive dysfunction, neuromuscular dysfunction, and seizure.
3. Treat primary hypoparathyroidism with calcium and vitamin D.
4. Treat to obtain a target serum calcium level in the low normal range (~ 2.00 to 2.13 mmol/L).
5. Monitor for a target 24-hour urinary calcium excretion rate of 2.5 to 3.75 mmol daily.

Clinicians should remain aware that treatment with calcium supplements and vitamin D analogs increases the risk of hypercalciuria, which in turn can lead to nephrolithiasis, nephrocalcinosis, and decreased renal function.

The recent FDA approval of recombinant human (rh) PTH(1-84) for the treatment of hypoparathyroidism adds PTH replacement therapy to the endocrinologist's assemblage to treat this chronic disease. [13-16]

Conclusion

The two cases described here show that primary hypoparathyroidism associated with intracerebral calcification can present in different ways. Various neuromuscular manifestations secondary to intracerebral calcification, hypoparathyroidism, and hypocalcaemia commonly occur. Presently, treatment consists of calcium supplementation and the use of vitamin D analogs, but The recent FDA approval of recombinant human (rh) PTH(1-84) for the treatment of hypoparathyroidism may play agreat role. Treatment is important to prevent progression of the disease.

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