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An elderly female with seizures and abnormal cerebral imaging

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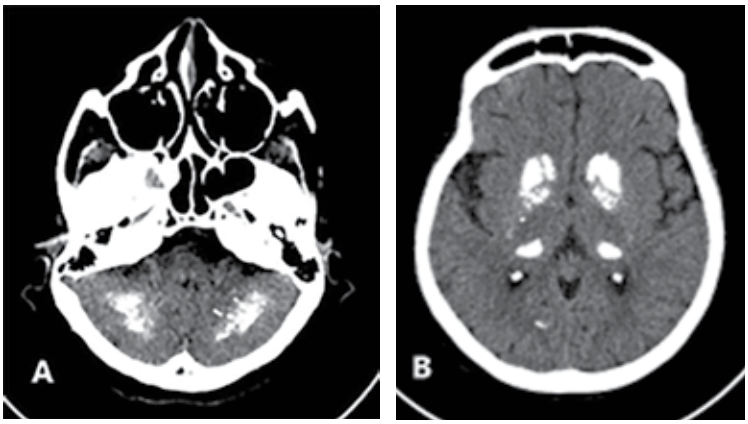
A 79-year-old female presented with two episodes of generalized tonic-clonic seizures within one day. Recovery was spontaneous for both seizures, occurring within about fi e minutes after the onset. She was well between the episodes with no associated fever, headache, or altered level of consciousness. She had undergone total thyroidectomy for a multinodular goiter about 30 years ago. About 15 years ago, she developed symptomatic hypocalcemia. She had received sodium valproate until four years ago for symptomatic epilepsy due to hypocalcemia. This had been discontinued since she became seizure-free with normalizing serum calcium.

She was also on levothyroxine, oral calcium carbonate, alfacalcidol, hydrochlorothiazide (HCT), and since of late her adherence to medications had become erratic.

On examination, she was alert and oriented. There was no Chvostek sign or Trousseau sign. The neurology examination was normal. Her pulse rate was 70/min and her blood pressure was 130/80 mmHg. The rest of the clinical examination was normal. Capillary blood glucose on admission was 115 mg/dL.

Urgent non-contrast computed tomography (NCCT) of the head is shown in figure 1.



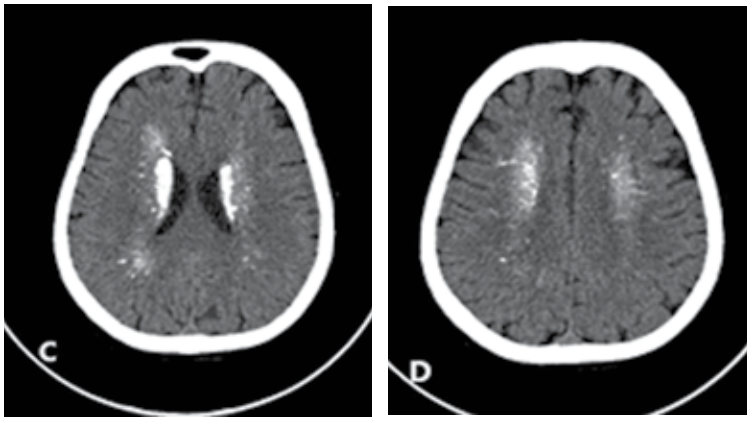


Figure 1 Non-contrast computed tomography

Figure 1: Axial views of the non-contrast computed tomography of the head of the patient demonstrating bilateral symmetrical calcifications of the dentate nucleus of the cerebellum (A), thalamus, and globus pallidus (B) caudate nucleus (C) and periventricular white matter (D).

What are the abnormalities seen in the CT scan?

There are extensive bilateral symmetrical hyperdensities suggestive of cerebral calcification involving the caudate nucleus, globus pallidus, thalamus, periventricular white matter of the frontal and parietal lobes, and dentate nucleus of the cerebellum.

What are the conditions associated with these imaging features?

This pattern of brain calcification with bilateral symmetrical basal ganglia and thalamus involvement (globus pallidus affected first) progressing to the other areas of the brain, including the cerebellum and subcortical white matter, is called 'Fahr syndrome' (1).

This can be due to underlying metabolic disorders such as hypoparathyroidism, pseudohypoparathyroidism, hyperparathyroidism, and other systemic disorders including mitochondrial disorders and infections. When there is no recognized etiology, this is attributed to primary familial brain calcification (termed Fahr disease) which is commonly inherited in an autosomal dominant manner. Her laboratory investigations at the time of presentation are summarised in table 1.

The patient was started on intravenous calcium gluconate infusion to correct severe hypocalcemia. She was started on oral sodium valproate as well.

Table 1 Summary of laboratory investigations at the time of presentation

Investigation	Result	Reference range
Serum Creatinine (mg/dL)	1.11	0.5-1.1
Sodium (mmol/L)	141	135-145
Potassium (mmol/L)	2.9	3.5-5.1
Total corrected Calcium (mg/dL)	3.5	8.5-10.2
Phosphate (mg/dL)	5.9	3-4.5
Magnesium (mg/dL)	1.4	1.7-2.2
Intact Parathyroid Hormone level (pg/mL)	3.4	14-65
Aspartate transaminase (U/L)	60	<40
Alanine transaminase (U/L)	26	<40
C-reactive protein (mg/L)	3.89	<5
Thyroid-stimulating hormone (mIU/l)	7.6	0.5-4.7
Urinalysis	Normal	

What is the most likely diagnosis in this patient?

Very low serum calcium with elevated phosphate in the presence of normal renal functions suggests impaired parathyroid hormone action. Low levels of intact parathyroid hormone suggest the underlying etiology to be primary hypoparathyroidism. Given the history of previous total thyroidectomy, the most likely cause is iatrogenic hypoparathyroidism. Hypokalaemia and hypomagnesemia, which were attributed to thiazide diuretics, resolved after the cessation of the agent.

What is the clinical significance of cerebral calcification in this patient?

In patients with hypoparathyroidism, there is no clear association between cerebral calcifications and neuropsychological manifestations including seizures, movement disorders, or cognitive impairment. It has been shown that most of the neuropsychological problems in hypoparathyroidism have a better correlation with the degree and the duration of hypocalcemia (2). The exact mechanism of cerebral calcification in hypoparathyroidism is also not known. But, it has been shown that decreasing serum calcium/ phosphate ratio is associated with progression of cerebral calcification, suggesting a potential role of hyperphosphatemia (3).

How should the seizures be managed in this patient?

Normalizing serum calcium is the mainstay of the management. There is controversy regarding the role of antiepileptic agents. If the patient develops seizures even when normocalcaemic, then there is

a clear indication for anti-epileptics. If antiepileptic drugs are initiated, they should be withheld after achieving normoglycemia and a seizure-free interval, as it has been shown that there is only a low risk of seizure recurrence (4).

How should the metabolic abnormalities be managed in this patient in the long term?

Long-term management of a patient with hypoparathyroidism commonly targets maintaining low-normal serum calcium levels while keeping the phosphate levels within the normal range. Measures should also be taken to minimize hypercalciuria. The common strategies used include (5),

- Replacement of calcium and active vitamin D (alfacalcidol or calcitriol). Calcium carbonate is the preferred agent as it additionally acts as a gut phosphate binder and helps to control hyperphosphatemia.
- Normalize serum vitamin D levels using cholecalciferol if the patient is having vitamin D deficienc .
- Serum calcium, phosphate, magnesium, creatinine, and urinary calcium excretion (24-hour urinary calcium and creatine excretion) should be monitored.
- Thiazide diuretics can be added if it is difficult to achieve near-normal calcium levels without marked hypercalciuria. Since this patient has
- low potassium and magnesium while on HCT, amiloride, potassium, and magnesium sparing diuretic can be added.
- In selected patients where control becomes difficult despite good adherence to treatment, recombinant human PTH 1-84 (rhPTH) can be considered. Difficulties in controlling include, not achieving calcium and phosphate targets, the need for very high doses of calcium and active vitamin D, and hypercalciuria. However, availability and cost are major issues when using rhPTH.

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