Case study

Fahr's Syndrome Secondary to Hypoparathyroidism Presenting with Paralysis and Recurrent Seizures: A Case Report.

ABSTRACT

Introduction: Fahr's syndrome (FS) is a rare neurodegenerative disorder characterized by bilateral and symmetrical calcification of basal ganglia (BG) and other brain structures. It can present with miscellaneous neuropsychiatric clinical manifestations. The diagnosis is confirmed by neuroimaging studies such as a head computer tomography (CT) scan or magnetic resonance imaging, which displays the calcification of BG and other structures in a bilateral and symmetrical pattern.

Case presentation: A 63-year-old female with a previous history of total thyroidectomy and quadriplegic paralysis presented to our hospital with altered mentation and recurrent generalized tonic-clonic seizures. Laboratory evaluation revealed hypocalcemia, hypokalemia, and hypoparathyroidism. Imaging with head CT was consistent with FS, demonstrating bilateral, symmetrical, and extensive calcification of BG, corona radiata, and cerebellar hemispheres with ventricular enlargement. Association with post-surgical hypoparathyroidism and relevant laboratory findings concluded the suspicion of etiology of ectopic calcification.

Conclusion: Our case represents a long-term consequence of untreated post-surgical hypoparathyroidism, which has consequently led to irreversible secondary FS. Maintenance of eucalcemic and euphosphatemic states is essential to prevent the progression of ectopic cerebral calcification.

Keywords: Fahr's syndrome, Fahr's disease, hypoparathyroidism, basal ganglia calcifications.

1. INTRODUCTION

Fahr's syndrome (FS) is a rare neurodegenerative disease characterized by symmetrically- and bilaterally-distributed calcification at the brain parenchyma. Its primary form, Fahr's disease (FD), is distinguished from FS by the absence of identifiable secondary etiologies. It has been attributed to autosomal dominant pattern of inheritance (1). The calcification is classically distributed bilaterally at the basal ganglia (BG), dentate nuclei, cerebellum, and subcortical white matter (2). Its prevalence is estimated to be approximately 1/1,000,000 (1–3). Other terminologies that are frequently used to describe FS include bilateral striopallidodentate calcification, bilateral basal ganglia calcification (BBGC), and calcinosis nucleorum (1–3).

Neurological manifestations of FS are variable and may include seizures, memory impairment, neuropsychiatric manifestation, movement, and speech problems. Other

manifestations include headache, orthostatic hypotension, vertigo, and papilledema secondary to increased intracranial pressure (ICP) (4).

2. PRESENTATION OF CASE

A 63-year-old female was brought to the emergency department (ED) with altered mentation and worsening bilateral extremity weakness for 2 days. She was a known case of a prior cerebrovascular accident and uncontrolled hypertension. She was also reported to exhibit recurrent generalized jerky involuntary movements. The family denied the presence of fever, difficulty breathing, vomiting, change in urine color, and urinary frequency.

Her past medical history was notable for hospital admission 1 month ago due to right-sided weakness. The admission was also complicated with urinary retention and episodes of urinary tract infections. In addition, the patient underwent a total thyroidectomy 30 years ago. The post-surgical period was complicated with hypocalcemia with suspected post-surgical hypoparathyroidism. Her routine medications include levothyroxine 100 µg/day and supplemental calcium. Family history was irrelevant.

On physical examination, the patient appeared obtunded; her Glasgow Coma Scale (GCS) was E1V2M4. Vital signs showed blood pressure (BP) of 120/50 mmHg, heart rate (HR) of 90 beats/min, respiratory rate (RR) of 24/min, temperature of 36.6°C, and oxygen saturation (SpO2) of 97% on room air. Neurological examination displayed spastic paralysis on the right extremities and hyperreflexia. Sensory functions were difficult to assess. In addition, laboratory evaluations revealed normocytic anemia with normal total leukocyte and thrombocyte counts. Electrolyte values were notable for K+ of 2.6 mg/dL (N: 3.5 – 5.1 mg/dL) and Ca^{2+} of 8.0 mg/dL (N: 8.5 – 10.5 mg/dL). In addition, thyroid function tests were within normal range. Her serum vitamin D concentration was normal, while the parathyroid hormone (PTH) was 5.5 pg/mL (N: 8.7 – 79.6 pg/mL).

An anteroposterior chest radiograph was only notable for cardiomegaly. Furthermore, non-contrast computed tomography (CT) scan **(figure 1)** demonstrated hyperintense foci distributed bilaterally on the BG, corona radiata, and cerebellar hemispheres, indicating a possible calcification process. Bilateral ventricular enlargement was also noted. Correspondingly, the patient is diagnosed with FS secondary to chronic inadequately-treated post-surgical hypoparathyroidism.

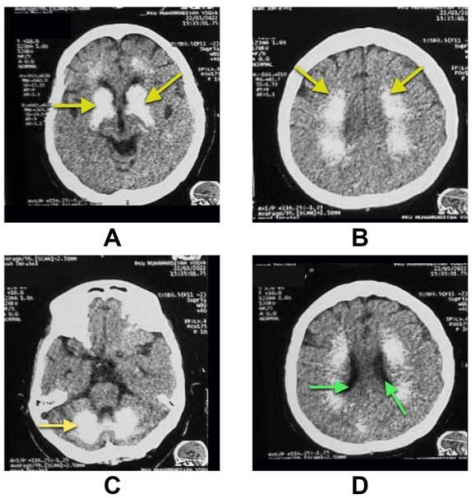

Figure 1: Head CT scan of the patient showing bilateral and symmetrical calcification of the BG (A), corona radiata (B), and cerebellar hemispheres (C). There is a mild bilateral dilatation of lateral ventricles (D).

Upon arrival and initial assessment, the patient was positioned 30° head-up with a sniffing position. The airway patency was secured by the nasopharyngeal airway with 4

liters per minute of oxygen. A nasogastric tube, peripheral intravenous (IV) cannula, and urinary catheter were inserted. Pharmacological management included IV mannitol 100 mL 6 hourly, IV dexamethasone 10 mg 8-hourly, IV phenytoin 150 mg 8-hourly, IV paracetamol 1 g 8-hourly, and correction of serum electrolytes.

Routine monitoring of hemodynamic status, electrolyte concentrations, and frequency of seizures was carried out intensively and treated accordingly. On the 6th day of admission, the frequency of seizures had significantly decreased. However, the patient was noted to experience shortness of breath, appeared distressed, and febrile. Vital signs showed HR of 107/min, RR of 30/min, temperature of 38°C, SpO2: 97%, and BP of 114/64 mmHg. Routine blood tests showed leukocytosis with predominant neutrophilia. The patient was diagnosed with hospital-acquired pneumonia (HAP) and was given ciprofloxacin 200 mg IV 12-hourly and ceftazidime 1 g 8-hourly IV.

Alas, on the 8th day of treatment, the patient experienced apnea, the carotid pulse was not palpable, pupils were fixed and dilated, and the electrocardiogram showed no electrical activity. After resuscitative attempts, the patient was subsequently declared dead secondary to HAP.

3. DISCUSSION

The term BBGC was first described by Delacour et al. in 1850 to illustrate a postmortem brain biopsy finding of bilateral calcification of the BG and its vasculatures in a 56-year-old patient presenting with lower limb paralysis (5). However, the condition is nowadays more eponymously known as Fahr's syndrome, which refers to Theodor Fahr, a German pathologist who reported similar pathological findings in 1930 in an 81-year-old patient presenting with dementia and paralysis (6). The association of FS with hypoparathyroidism was first described by Eaton et al. in 1939 (7).

In contrast to the described pathogenesis of ectopic mineralization in FD that occurs mainly due to dystrophic calcification, the mineralization FS, such as in the setting of hypoparathyroidism, is thought to be triggered via metastatic calcification as a consequence of systemic mineral imbalance (4,8). Albeit the pathogenesis of cerebral calcification in a hypocalcemic milieu such as hypoparathyroidism is not completely understood, some proposed hypotheses include the decrease in calcium/phosphate ratio and subsequently elevated serum calcium-phosphate products (9). Another suggested theory is an increased expression of osteogenic molecules in hypoparathyroidism, including osteonectin and osteopontin, with its predilection in caudate nuclei (10).

Our patient presented with right hemiparesis, spasticity, and generalized tonic-clonic seizures. Kalampokini et al. (11) reviewed 233 case reports of hypoparathyroid FS and showed that the common clinical presentations include tetany (51.4%), motor disturbance (48.4%), seizures (46.5%), and neuropsychiatric manifestations. Parkinsonism contributed to the majority of the motor abnormalities. Overlaps of symptoms were observed, such as the mixed presentation of hypokinesia, cognitive deficits, and cerebellar defects (3,11). Diagnostic criteria have been proposed by Perugula et al. (1) and Saleem et al. (2) **(table 1)**, incorporating neurological manifestations, associated comorbidities, and imaging findings on the CT scan or magnetic resonance imaging. In addition, single proton emission computed tomography may also show significantly reduced perfusion to the calcified brain areas.

Table 1: Diagnostic Criteria of Fahr's Syndrome (FS) and Fahr's Disease (FD) (1–3)

	Consider the diagnosis of FS or FD in the presence of some or all of the following presentations:	
	Basal ganglia (BG) movement disorder (extrapyramidal). Cognitive disturbance. Cerebellar disorder. Psychiatric presentation.	Pyramidal signs. Gait abnormalities. Speech dysfunction. Sensory changes.
	Consider the diagnosis of FD if:	**Consider the diagnosis of FS if:**
Age	40-60 years	30-40 years
Associated conditions	Positive family history Associated autosomal dominant or recessive pattern of inheritance	**Any of the following endocrinopathies:** idiopathic or secondary hypoparathyroidism, pseudohypoparathyroidism, pseudopseudohypoparathyroidism, hyperparathyroidism **and** **One of the following conditions:** - Congenital brucellosis - Neuroferritinopathy - Tuberous sclerosis - Mitochondrial myopathy - *Lipoid proteinosis*
Pattern of calcification	Coarse, progressive, symmetrical, and bilateral calcification of BG.	Symmetrical and bilateral intracranial calcification
Management	Symptomatically-directed treatment No definitive therapy.	The treatment is aimed at the underlying pathology Symptomatic therapy adjunctively

Heretofore, there is no known definitive therapy for FS. The management is generally aimed at alleviating the presenting symptoms. Nevertheless, in cases of FS with an identified secondary etiology, treatment needs to be focused on addressing the underlying primary pathology, with symptomatic management as adjunctive therapy. Therefore, early diagnosis of secondary FS is essential to prevent further progression of FS and potentially reverse the pathology of intracranial calcifications. Goswami et al. (9) reported that the evidence of BG calcification is approximately 73.8% in patients with idiopathic hypoparathyroidism (IH). BG calcification in cases of IH is also correlated with the duration of hypocalcemia and the value of the calcium/phosphate ratio. Thus, improvement of serum calcium as well as calcium/phosphorus ratio needs to be done early to prevent the development of secondary FS. There is evidence showing that for every 1% increase in the calcium/phosphate ratio during follow-up, the probability of developing BG calcification decreased by 5% (9).

The conventional cornerstone therapy for hypoparathyroidism involves calcium and vitamin D supplementation **(table 2)** (12,13). The European Society of Endocrinology (ESE) and the American Association of Clinical Endocrinologists guidelines recommended to maintain serum calcium in hypoparathyroidism at the lower normal range, i.e. 8–9 mg/dL, as long as the patient is free of symptoms of hypocalcemia (12–14). Calcium carbonate is generally preferred to calcium citrate because it has more elemental calcium by molecular weight (40% vs 21%). However, calcium citrate is preferred in the elderly population, especially those taking antacids, proton pump

inhibitors, or those with low gastric acidity, as gastric acidity is not essential for the absorption of calcium citrate. The general dose of calcium carbonate is 1 to 2 g given in divided doses of 500 mg each time, although some cases require up to 9 g per day (13). High doses of calcium should be avoided because it can increase the risk of long-term complications such as impaired renal function and ectopic calcifications (13,14). The 24-hour urinary calcium and creatinine should be monitored every 6 months to once a year to monitor for hypercalciuria.

Table 2. Recommended therapy in hypoparathyroidism

Drug	Dose	Comments
Calcium supplementation		
Calcium carbonate	1 – 9 g/day in 2 – 4 divided doses	Necessitates a high stomach acidity for absorption Requires to take with a meal for optimal absorption
Calcium citrate		Doesn't require a high stomach acidity and prior meal for its absorption
Vitamin D supplementation		
Ergocalciferol (D2) or Cholecalciferol (D3)	400-800 IU/day	
Calcitriol	0.25–2.0 µg/day	
Alfacalcidiol	0.5–4.0 µg/day	
Adjuvant therapy		
Hydrochlorothiazide	12.5-100 mg/day	Consider as adjuvant therapy for hypocalcemia; act mainly reduce the urinary calcium excretion in the evidence of hypercalciuria.
Chlorthalidone	25-100 mg/day	
Indapamide	1.25-5 mg/day	
Amiloride	5 mg/day	

Furthermore, the ESE recommended calcitriol as a vitamin D supplement because the conversion of vitamin D to its active form via the kidneys might be impaired in hypoparathyroidism (14,15). However, calciferol, especially cholecalciferol, can be used if calcitriol is not available. There is also some evidence to support the use of calciferol in conjunction with calcitriol due to the association of low vitamin D levels with negative effects on bone and extraskeletal health (16). Therefore, ESE also recommended vitamin D supplementation at a dose of 400-800 IU/day.

A promising treatment for hypoparathyroidism is the use of PTH analogs, including teriparatide (PTH 1-34) and recombinant human PTH 1-84 (rhPTH 1-84). Both PTH (1-34) and PTH (1-84) have been shown to reduce the need for vitamin D supplementation and increased markers of bone turnover (17). Importantly, teriparatide administration has been evaluated for the treatment of hypoparathyroidism in both the adult and pediatric populations and appears to be safe and efficacious in improving urinary calcium concentrations, serum calcium levels, and quality of life (18-19). Meanwhile, rhPTH 1-84 was approved by the FDA in 2015 as an adjunctive therapy for hypoparathyroidism in individuals who are not adequately controlled with conventional therapy. The REPLACE study, a randomized, double-blind, placebo-controlled clinical trial conducted in 134 adults with hypoparathyroidism showed that 53% of subjects treated with rhPTH 1-84 reduced supplemental calcium and active vitamin D by >50%, with 43% of subjects able to completely discontinue all vitamin D supplements and reduce her calcium dose to <500 mg/d and maintain normal serum calcium (20). Indications for the use of the proposed PTH analogs are listed in **Table 3**.

Table 3. Indication to consider the administration of rhPTH 1-84 in hypoparathyroidism (17)
1. Poor control of serum calcium (corrected serum calcium: <7.5 mg.dL) or clinical symptoms. 2. Oral calcium supplementation > 2.5 g/day or 1,25-(OH)D > 1.5 mcg/day or 1-alpha vitamin D > 3.0 mcg/day. 3. Hypercalciuria, nephrolithiasis, nephrocalcinosis, reduced creatinine clearance or eGFR (<60 mL/min), or increased risk of stones by biochemical analysis of urine. 4. Hyperphosphatemia or calcium-phosphate products >55 mg/dL (4.4 mmol/L) 5. Gastrointestinal dysfunction due to intrinsic disease or after bariatric surgery 6. Reduced quality of life

4. CONCLUSION

FS is a rare syndrome characterized by bilateral and symmetrical calcifications in the BG. Hypoparathyroidism is one of the important risk factors for secondary FS. FS secondary to hypoparathyroidism is potentially preventable if hypocalcemia is properly controlled. Duration of hypocalcemia and low calcium/phosphate ratio in FS are considered to be the best predictors of the development of BG calcification in cases of hypoparathyroidism. Management with calcium, vitamin D supplementation, and adjunctive therapy is needed to prevent acute symptoms and long-term complications. PTH analogs may also be considered in recalcitrant cases. Our patient's case was a long-term consequence of permanent postoperative hypoparathyroidism which was not adequately managed to maintain the eucalcemic state.

CONSENT

Written informed consent was obtained from the patient’s relative for the publication of this case report and accompanying images.

ETHICAL APPROVAL

As per international standards or university standards, written ethical approval has been collected and preserved by the authors.

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