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Case Report

Fahr syndrome and neurological manifestations in hypoparathyroidism patients ☆,☆☆

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ABSTRACT

Fahr syndrome is an uncommon (prevalence < 1/1.000.000) neurological disorder characterized by abnormal calcified deposits in the basal ganglia, nucleus dentatus, and cerebral cortex. These calcification can lead to various neurological manifestations. Distinguishing Fahr syndrome from Fahr disease is crucial due to differences in their etiology, location of lesions, prognosis, and therapy. Currently, Fahr disease lacks a specific treatment, while Fahr syndrome requires target intervention based on the underlying cause. A 35 years old female patient was presented to the emergency department with recurrent tonic-clonic seizures followed by the decreased consciousness. The patient had history of thyroidectomy surgery 7 years before, behavioral disturbances, hallucinations for past 1 week, and cataracts in both eyes. Laboratory examination showed low calcium levels (4 mg/dL), which can trigger seizures, and low PTH levels, indicating hypoparathyroid. A head CT scan without contrast displayed extensive bilateral calcification, particularly in the basal ganglia. Following stabilization, an EEG recording discovered diffuse encephalopathy. The patient received seizure management and maintenance medication of calcium with vitamin D. During the 3 months follow up, no sign of relapses were observed. Intracranial calcifications are often physiological but should be suspected as pathology in certain symptoms and calcification patterns. The presence of multiple intracranial calcifications, specifically in the basal ganglia, indicates Fahr disease or Fahr syndrome, which can cause various neurological manifestations. One of the etiologies of Fahr syndrome to consider is hypoparathyroid. Therefore, identifyisng and managing this etiology is crucial for preventing the progression of Fahr syndrome.

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Introduction

Fahr syndrome is a rare disease with a prevalence of < 1/1,000,000. Furthermore, it was characterized by neurological disorders resulting from abnormal intracranial calcification deposits in the basal ganglia, dentate nucleus, and cerebral cortex. This condition was initially described by German neurologist Karl Theodor Fahr in 1930. Fahr syndrome is different from Fahr disease, as it is caused by secondary factors, while Fahr disease arises from a primary hereditary condition [1]. This case report presents Fahr syndrome secondary to hypoparathyroidism, which developed as a complications of thyroidectomy surgery that highlight the essential to differentiate Fahr syndrome and Fahr disease.

Case report

A 35-year-old female presented with complaints of generalized tonic clonic seizures. The seizures followed the same pattern, with a duration of approximately 5 minutes and no signs of regaining consciousness between episodes. The first seizure occurred 2 years ago with the same characteristics as the current condition. In the past year, the patient experienced seizures at least once a month, but it has become more frequent in the last 2 months. Furthermore, thyroidectomy surgery was conducted 7 years ago and euthyrox was administered, with no prior use of antiseizure medication.

Upon examination, the patient exhibited a Glasgow Coma Scale (GCS) score, blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature of 315, 111/69 mmHg, 69 beats per minute, 18 breaths per minute, 97% with a 2-liter-per-minute nasal cannula, and 37 degrees Celsius, respectively. Cataracts were observed in the both eyes during the physical examination. Neurological examination showed a decreased consciousness without signs of meningeal irritation, and no focal neurological deficits were observed, with negative pathological reflexes. The patient exhibited a positive Chvostek's sign, carpopedal spasms, and a positive Trousseau's sign indicating hypocalcemia sign.

In the last month, the patient had showed behavioral changes, including frequently laughs, self-talk, and unexplained crying. Furthermore, there were visual and auditory hallucinations in the form of her father's shadow and encouraging voice.

Based on electrocardiogram (ECG) examination, there was a prolongation of the QT interval suggestive of hypocalcemia. Laboratory tests showed hypocalcemia (4 mg/dL, normal range 8.5-10.5 mg/dL), hyperphosphatemia (7.22 mg/dL, normal range 2.5-4.5 mg/dL), hypomagnesemia (1.2 mg/dL, normal range 1.8-2.4 mg/dL), and hypokalemia (2.9 mg/dL, normal range 3.5-5.0 mg/dL). HBsAg, Anti-HCV, ANA test were non-reactive and Complement C3, Complement C4 were within normal limits. The parathyroid hormone (PTH) level was low (2.21 pg/mL, normal range 10-65 pg/mL), while a non-contrast CT (Computed Tomography) scan of the head indicated bilateral symmetric calcifications in the basal ganglia, periventricular regions, gray and white matter junction, right and left fronto-temporoparietal lobes, as well as right and left cerebellar hemispheres (Figure 1). Electroencephalogram (EEG) recording showed abnormal results with background slow activity and generalized continuous slow activity (Figure 2). Additionally, it indicated moderate diffuse encephalopathy.

Table 1 – Laboratory findings summary.

Examination	Values in the patient	Normal values
Complete blood count		
Hb (g/dL)	11.3	11-14.7
Leukocytes ($10^3/\mu L$)	6.42	3.37-10
Platelets ($10^3/\mu L$)	386	150-450
Electrolytes		
Sodium (mmol/L)	140	135-145
Potassium (mmol/L)	2.9	3.5-5
Chloride (mmol/L)	95	98-107
Magnesium (mg/dL)	1.2	1.8-2.4
Calcium (mg/dL)	4	8.5-10.5
Phosphate (mg/dL)	7.22	2.5-4.5
Hormones		
PTH (pg/ml)	2.21	10-65
FT4	0.76	0.83-1.43
TSH	22.965	0.02-132.7
Liver function		
SGOT (U/L)	378	0-37
SGPT (U/L)	302	0-55
Kidney function		
BUN (mg/dL)	18.5	7-20
Kreatinin (mg/dL)	0.9	0.5-1.2
Others		
ANA test	Negative	Negative
C3 (mg/dL)	99	82-185
C4 (mg/dL)	40	15-53
Albumin (g/dL)	4.17	3.4-5

Based on the presented clinical features, this case leans more towards Fahr syndrome. This was because at young age, the patient had secondary hypoparathyroidism with a history of thyroidectomy surgery, neuropsychiatric manifestations (seizures, behavioral disturbances, and cognitive impairments), hypocalcemia-related manifestations (cataracts, Chvostek's sign, carpopedal spasms, Trousseau's sign, and QT interval prolongation on ECG) (Figure 2, A and B), laboratory findings of hypocalcemia, hyperphosphatemia, and low PTH levels (Table 1). Additionally, symmetric bilateral intracranial calcifications was observed in the basal ganglia on imaging. Autoimmune tests such as ANA test and complement C3, C4 yielded normal results (Table 1, C). According to the above outcomes, the patient was diagnosed with Fahr syndrome due to secondary hypoparathyroidism related to complications of thyroidectomy surgery.

The primary goal of treatment was to control calcium levels within the normal limits. Management of hypocalcemia in the patient includes the use of vitamin D and calcium supplementation. After a 3-month follow-up, no signs of seizures were observed.

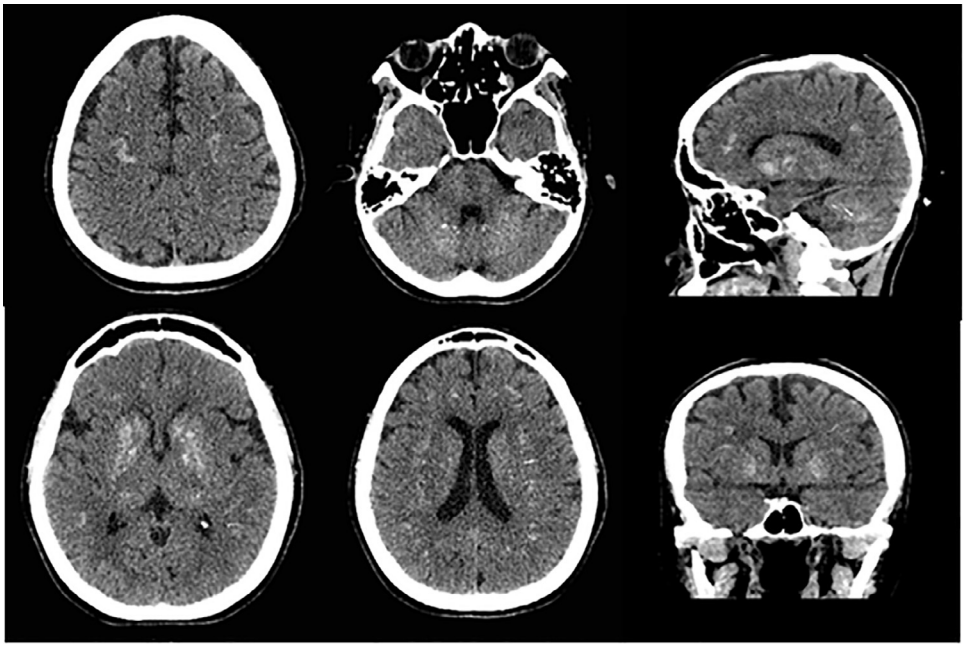

Figure 1 – Noncontrast CT scan of the head in the patient shows bilateral, symmetric calcifications in the right and left basal ganglia, right and left periventricular regions, gray and white matter junction, right and left fronto-temporoparietal lobes, as well as right and left cerebellar hemispheres.

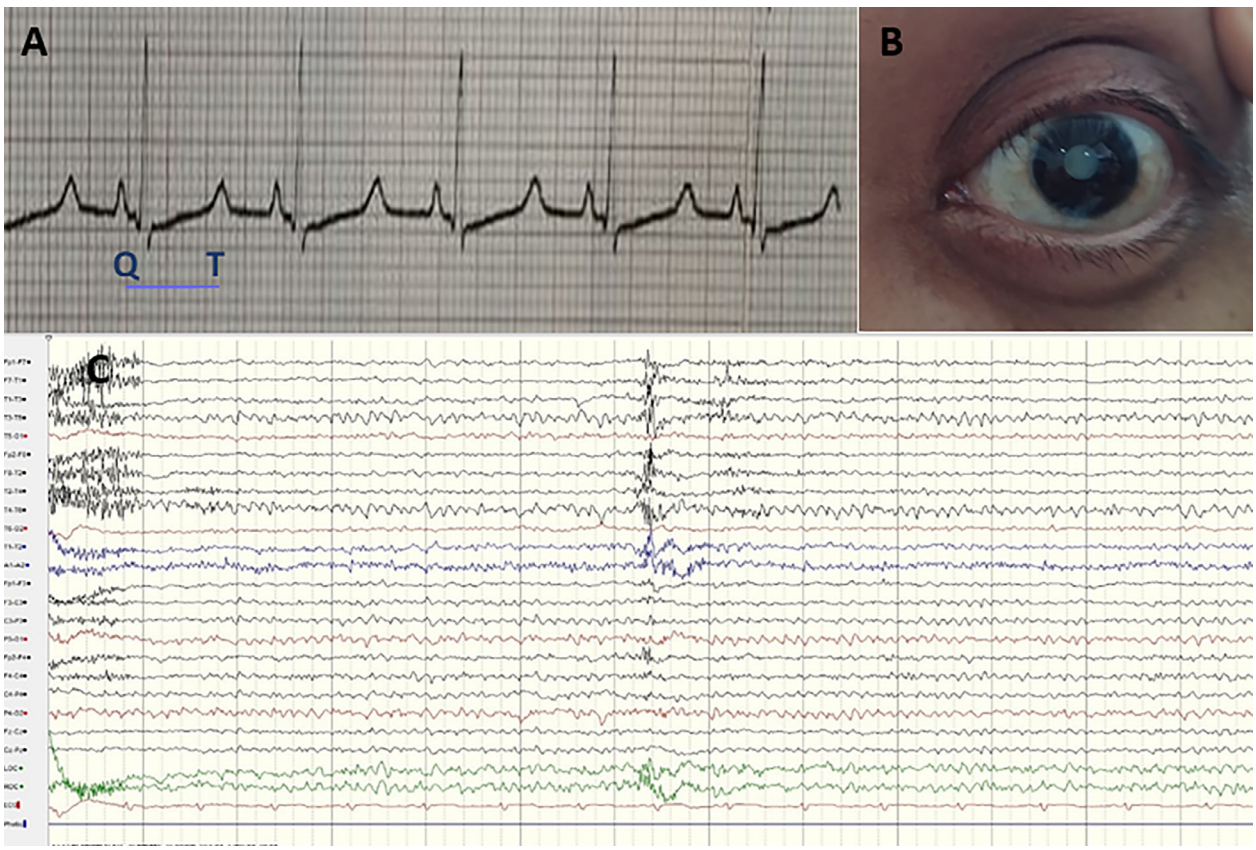

Figure 2 – (A). ECG shows a sinus rhythm at 75 beats per minute with prolong QT interval. (B) Cataract in the patient's eye. (C) EEG shows features of diffuse encephalopathy.

Discussion

Fahr disease and Fahr syndrome, presents similar clinical manifestations. Furthermore, these conditions should be suspected when there are movement disorders in the basal ganglia, pyramidal symptoms, cognitive impairments, gait disturbances, cerebellar abnormalities, speech dysfunction, psychiatric symptoms, and sensory changes. Consider Fahr syndrome typically presents in individuals aged 30-40 years and is characterized by symmetric bilateral intracranial calcifications and an underlying disorder. Fahr disease is more commonly observed in individuals aged 40-60 years, with progressive symmetric bilateral calcification in the basal ganglia and autosomal dominant or recessive genetic factors. Fahr syndrome has a specific treatment related to the underlying cause, with symptomatic therapy as an additional option. Meanwhile, effective therapy for Fahr disease is currently unavailable [2].

One of the most common causes of Fahr syndrome is hypoparathyroidism. Physiologically, the parathyroid glands secrete parathyroid hormone (PTH) to regulate calcium and phosphorus in the body. Hypoparathyroidism occurs when the production of PTH is reduced, resulting in hypocalcemia and hyperphosphatemia. Furthermore, it has various causes, with the most common being thyroid surgery, but only 1%-5% of this condition become permanent cases. Permanent hypoparathyroidism leads to chronic hypocalcemia, which can result in various clinical manifestations such as paresthesia, spasms (tetany), positive Chvostek sign, parkinsonism, extrapyramidal symptoms, cataracts, and QT interval prolongation on EKG recording. Additionally, severe hypocalcemia (calcium $<$ 5 mg/dL) can result in seizures and cardiac arrhythmias [2–4]. Meanwhile as for the Fahr disease, the calcium serum and PTH remains normal [5].

Seizures in cases of Fahr syndrome caused by hypoparathyroidism can be caused by both hypocalcemia and calcifications in the cortical regions. The association between cortical calcifications and epileptic seizures is evident in cases of neurocysticercosis and Sturge-Weber Syndrome (SWS). Calcified area can lead to abnormal vascular disturbances, hence, causing suboptimal perfusion [6,7]. Some studies suggested that calcifications in the basal ganglia play a role in the propagation and modulation of epilepsy. It was hypothesized that basal ganglia act as an inhibitory circuit in epileptic seizures. Calcium deposits in this nuclei structures may disrupt inhibitory circuits and make hypocalcemic patients susceptible to epileptic seizures [8]. Hypocalcemia can result in seizures without tetany because excessively low calcium concentrations increases cell excitability through the Calcium Sensing Receptor (CaSR) and various other ion channels. Reduced tissue perfusion, disturbances in inhibitory circuits, and cellular hyperexcitability contribute to the development of seizures [9].

The reduction in PTH results in hyperphosphatemia and hypocalcemia, which can lead to ectopic calcifications [1]. Histopathological studies indicate that calcium is the major element responsible for the radiological appearance of intracranial calcifications. Other minerals, including iron, magnesium, aluminum, and zinc also play a role. The reactive astrocytes and microglia accumulated around calcification deposits suggest an ongoing mild inflammatory process. Additionally, calcification can be observed within the tunica media of arteries, arterioles, and capillaries, potentially obstructing the lumen. Further analysis of the blood-brain barrier showed extravasation and perivascular fibrinogen deposits, which may be associated with calcified areas [10]. It takes around 8-10 years to cause basal ganglia calcification from hypoparathyroidism alone. Intracranial calcification may worsen with advancing age and unregulated calcium serum level [4,11].

There is still limited data regarding significance between Fahr disease or Fahr syndrome with cardio and cerebro vascular disease (CVD). Some case reports (incidence of stroke in young patient with Fahr disease) and literature review supports the pathogenic role of Fahr disease with CVD due to extensive calcium and mineral deposits in affected vessels leading to reduction of vascular elasticity and hemodynamic changes, although the exact pathogenic mechanism is still unclear [12,13]. Another case report found the incidence of Fahr syndrome with cardiomyopathy. Calcium is necessary for myocardial contractile function, while parathyroid hormone has a positive inotropic effect on the heart muscle, thus hypocalcemia and hypothyroidism in Fahr syndrome may lead to cardiomyopathy [14]. A causal link between Fahr disease and CVD needs further investigation.

The long-term management goal for hypoparathyroidism was to maintain serum calcium levels within the low-normal range, along with serum phosphorus levels in the high-normal range, while avoiding significant hypocalcemia, or hypercalcemia. The management target was to reduce symptoms, minimize the risk of kidney stones and dysfunction, as well as prevent ectopic calcium deposition in tissues. Daily treatment with calcium and active vitamin D was necessary to achieve the desired serum calcium levels. In cases of severe hypocalcemia, calcium correction was achieved through intravenous calcium gluconate injections [2,7]. Meanwhile for the Fahr disease, genetic mutation is the main pathology and currently there is still no specific treatment. Despite normal calcium level in Fahr disease, vitamin D might be potential treatment. The Vitamin D might reduced intracranial calcification through bind to SLC20A2 gene and upregulate SLC20A2 mRNA, the gene mutation in Fahr disease that disrupted brain metabolism. This mechanism might inhibit the progression of Fahr disease patient [15].

Eventhough maintaning calcium in normal level significantly correlate with seizure suppresion, Fahr's syndrome can be a cause of epileptic seizures and antiepileptic drug (AED) therapy should be considered. Presently there are still no specific guidelines regarding the efficiency of the antiepileptic treatment for patients with cerebral calcifications and hypocalcemia, as we seen in fahr syndrome caused by hypoparathyroidism [16]. However, there are some AED therapy, particularly long-term treatment, that known to be associated with vitamin D deficiency (eg, phenobarbital, phenytoin, and carbamazepine), leading to worsen hypocalcemia. Levetiracetam does not seem to have adverse effect on hypocalcemia and vitamin D deficiency, thus should be considered to give on

epileptic patient with risk of hypovitamin D and hypocalcemia [17,18].

Intracranial calcifications occured physiologically or pathologically, typically resulting from the deposition of minerals (such as calcium) or metals (such as iron) in blood vessels, glands, cortex, or other brain structures. CT scans were the most sensitive imaging modality for detecting intracranial calcifications [19]. The prevalence of calcifications varies, ranging from 1% in young individuals to 20% in the elderly. Physiological calcifications were common in the pineal gland, choroid plexus, habenula, falx cerebri, and cerebellar tentorium. The pineal gland was the most frequent site, followed by the choroid plexus. Pathological calcifications should be suspected when calcifications occured in rare locations, exhibit expansion, or cause symptoms in patients. Furthermore, it can be caused by vascular, neoplastic, genetic, infectious, metabolic, inflammatory, and neurotoxic factors [20]. As for the Fahr disease the calcification occured from genetic mutation (SLC20A2 and XPR1), while Fahr syndrome occured from underlying disease [15].

Physiological calcifications in the basal ganglia had a prevalence of only 1.3%. Therefore, the presence of calcifications should raise suspicion of a pathological condition. Hypoparathyroidism was the most common cause of pathological calcifications in the basal ganglia. Other causes included Fahr disease, tuberous sclerosis, Cockayne's syndrome, and mitochondrial diseases [20]. The presence of intracranial calcifications in various locations can disrupt or dysfunction affective, extrapyramidal, and cerebellar functions, leading to various neuropsychological manifestations. This dysfunction may result from disruptions in the corticostriatal tract, which carries sensory input from the cerebral cortex to the striatum (caudate and putamen), then transmits it to the globus pallidus, where sensory input is refined and projected back to the cortex for organized activities [21,22]. Both Fahr disease and Fahr syndrome had similiarity location in intracranial calcification especially in bilateral basal ganglia [23].

Distinguishing physiological from pathological calcifications was crucial in patients diagnosis. Bilateral, symmetric, dense, and expansive calcifications in the basal ganglia were typically pathognomonic signs of Fahr disease or syndrome. Meanwhile, physiological basal ganglia calcifications related to age were usually small, minimal, asymmetric, and limited to the globus pallidus [10].

Conclusion

In conclusion, when intracranial calcifications are presented, it is imperative to make a careful distinction between their physiological and pathological origins. For radiological approach, the presence of symmetric, bilateral, and multiple calcifications in head CT Scan raised consideration of Fahr syndrome or Fahr disease. For clinical approach, hypocalcemia sign and history of thyroid surgery leads to Fahr syndrome. This case report highlight the essential to differentiate Fahr syndrome and Fahr disease based on their respective etiologies, as well as management of underlying causes. Effectively managing hypocalcemia through daily calcium and vitamin D treatment was pivotal in preventing the progression of Fahr syndrome originating from hypoparathyroidism.

Patient consent

A written, informed consent was obtained from the patient/legal representative for the publication of this case report (including all data and images).

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