Case Report

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Internal Medicine Section

Parkinsonism and Seizures in Fahr's Disease: A Report of Two Cases

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ABSTRACT

Fahr's disease, also known as primary familial calcifications, is a rare neurodegenerative disorder characterised by abnormal calcium deposits in the brain caused by genetic mutations. Fahr's syndrome, or secondary brain calcification, results from infections, metabolic, and endocrine abnormalities leading to calcium deposits in the brain. Although Fahr's disease and Fahr's syndrome are recognised as separate entities, they are often used interchangeably in the literature. The prevalence of Fahr's disease is <1 per 100,000, with no significant gender differences, and it often goes undiagnosed since one-third of the patients are asymptomatic. Patients may present with headaches, movement disorders, seizures, cognitive defects, and psychiatric manifestations, which are usually mistaken for other neurological conditions. The pathophysiology is still unclear but is postulated to be due to abnormal calcium and phosphate metabolism and transport in the brain. Fahr's disease can be diagnosed based solely on neuroimaging, even without an identifiable aetiology. While genetic testing is supportive, it is not mandatory, as many patients lack mutations despite a positive family history. Both conditions show characteristic symmetrical calcifications in the basal ganglia, as well as areas like the thalamus, cerebellum, and subcortical white matter on neuroimaging. Management primarily focuses on symptomatic treatment to control movement disorders, preserve cognition, and alleviate neuropsychiatric manifestations through a multidisciplinary approach. Through this case report, the authors highlight two cases with brain calcifications and their management. The first patient had parkinsonian features, while the second patient experienced a generalised tonic-clonic seizure and were diagnosed with Fahr's disease due to an unidentifiable aetiology and Fahr's syndrome due to hypoparathyroidism, respectively.

Keywords: Basal ganglia diseases, Brain calcifications, Hypoparathyroidism, Neurodegenerative disease

CASE REPORT

Case 1

A 65-year-old woman with uncontrolled diabetes reported experiencing progressively slower movements and increasing difficulty with daily activities such as walking, dressing, and clumsiness while eating over the past six months. She also experienced more frequent falls, slurred speech, and difficulty swallowing, all of which significantly impacted her daily life. The patient had a known case of diabetes mellitus for 10 years and was on Metformin 500 mg twice daily.

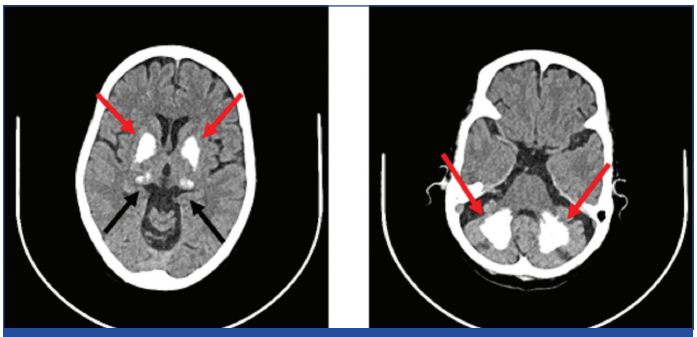
Upon examination, the patient displayed a mask-like face, slowness of voluntary movements, rigidity, resting tremors with a typical pill-rolling tremor in both hands, and a wide-based, unsteady gait. There was no loss of bowel or bladder control, sensory involvement, cranial nerve involvement, or decreased power in the limbs. No family history of similar complaints or neurological diseases was noted. Differential diagnoses included normal pressure hydrocephalus, Parkinson's disease (either idiopathic or vascular), and Parkinson-plus syndromes, such as progressive supranuclear palsy.

Laboratory investigations were within normal range, as mentioned in [Table/Fig-1]. A CT scan of the brain revealed symmetrical calcifications in the bilateral basal ganglia, thalamus, and cerebellum, as shown in [Table/Fig-2,3]. MRI of the brain revealed symmetrical calcifications in the basal ganglia, thalamus, corona radiata, and dentate nucleus of the cerebellum, as shown in [Table/Fig-4-6]. CSF analysis was negative for infections. Genetic analysis was not performed. The patient was diagnosed with Fahr's disease, which led to Parkinsonism, and was treated with levodopa-carbidopa, dual antiplatelet therapy, statins, physiotherapy, and speech rehabilitation. Subcutaneous insulin was added for better glycaemic control in addition to metformin. Upon review after three months, the patient showed partial improvement, with a reduction in tremors and improved mobility, although mild gait instability and slowness of movements persisted.

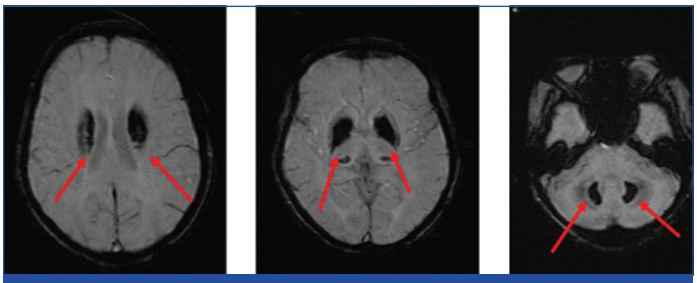
Test parameter	Test value	Reference range
Haemoglobin (Hb) (g/dL)	12	12.0-15.5
Packed cell volume (%)	36	36-48 (Female)
Mean corpuscular volume (fL)	85	80-100
White blood cell count (/µL)	7910	4000-11000
Neutrophils (%)	68.4	40-70
Lymphocytes (%)	27.1	20-40
Platelets (/µL)	280,000	150,000-450,000
Cholesterol (mg/dL)	311	<200
Triglycerides (TGL) (mg/dL)	65	<150
HDL-C (mg/dL)	32	>50
LDL-C (mg/dL)	73	<100
VLDL-C (mg/dL)	13	2-30
Fasting blood sugar (mg/dL)	76	70-100
Postprandial blood sugar (mg/dL)	247	<140
HbA1c (%)	9.6	<5.7
Urea (mg/dL)	26	15-40
Creatinine (mg/dL)	0.6	0.6-1.1
Total bilirubin (mg/dL)	0.58	0.5-1.0
AST (IU/L)	28	<31
ALT (IU/L)	25	<34
ALP (IU/L)	76	30-120
Total protein (g/dL)	6.8	6.6-8.3
Albumin (g/dL)	3.5	3.5-5.2
Sodium (Na) (mmol/L)	138	135-145
Potassium (K) (mmol/L)	4.4	3.5-5.0

Chloride (Cl) (mmol/L)	96	96-106
Bicarbonate (HCO3) (mmol/L)	30	22-29
Calcium (Ca) (mg/dL)	10.1	8.5-10.5
Phosphorus (PO4) (mg/dL)	3.3	2.5-4.5
Magnesium (Mg) (mg/dL)	2.2	1.7-2.4
TSH (µIU/mL)	3.12	0.4-4
Free T3 (pg/mL)	2.84	2.5-3.9
Free T4 (ng/dL)	1.14	0.58-1.64
Vitamin D3 (ng/mL)	25.65	30-100
Parathormone (pg/mL)	23.26	10-65

[Table/Fig-1]: Shows laboratory tests of case 1 with reference ranges.
HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein cholesterol; HbA1c: Glycosylated haemoglobin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TSH: Thyroid stimulating hormone



[Table/Fig-2,3]: CT scan of the brain in axial sections showing bilateral symmetrical calcifications mainly in the putamen and globus pallidus (red arrows), with some involvement in the thalamus (black arrows); and bilateral symmetrical calcifications in the cerebellum (red arrows), respectively. (Images from left to right)



[Table/Fig-4-6]: Susceptibility weighted images showing bilateral symmetrical calcifications in the corona radiata, basal ganglia and thalamus, dentate nucleus of the cerebellum, respectively. (Images from left to right)

Case 2

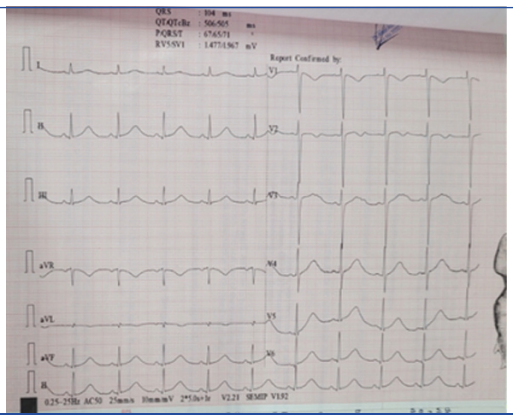
A 54-year-old female presented with generalised tonic posturing and rhythmic clonic movements in all four limbs, which were accompanied by up-rolling of the eyes and tongue biting. These symptoms lasted about five minutes and were followed by postictal confusion. There was no preceding aura or urinary incontinence. The patient had experienced tetany symptoms for the last three months. She did not have a history of fever, projectile vomiting, palpitations, paresthesia, or hallucinations. The patient had a history of hypertension and hypoparathyroidism secondary to a thyroidectomy, which she underwent 10 years ago. There was no history of seizures or neuropsychiatric diseases in her parents. Her routine medications included amlodipine 5 mg, thyroxine 100 mcg, and calcium 500 mg.

Neurological examination revealed Chvostek and Trousseau signs. There were no signs of meningeal irritation. Differential diagnoses included electrolyte abnormalities such as hyponatraemia and hypocalcaemia, meningitis, and intracranial space-occupying lesions secondary to infections or malignancy.

Blood investigations revealed hypocalcaemia (6.6 mg/dL), hyperphosphataemia (6.8 mg/dL), hypomagnesaemia (1.6 mg/dL), and low vitamin D3 levels (28.12 ng/mL), as detailed in [Table/Fig-7]. An Electrocardiogram (ECG) revealed QT prolongation, as shown in [Table/Fig-8]. Fundus examination using a direct ophthalmoscope showed no papilledema or retinopathy changes. A CT scan of the brain revealed symmetrical calcifications in the bilateral basal ganglia and cerebellum, as illustrated in [Table/Fig-9,10].

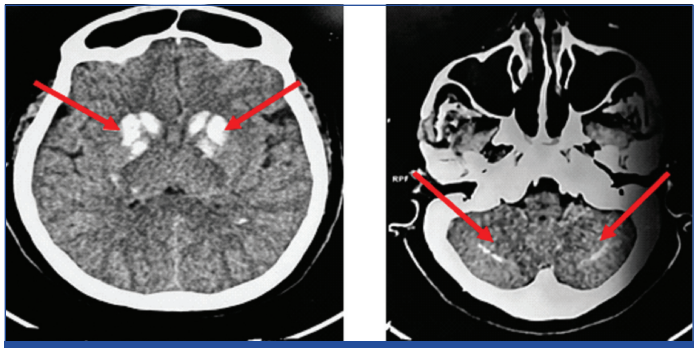
Test parameter	Test values	Reference range
Haemoglobin (Hb) (g/dL)	12.8	12.0-15.5
Packed cell volume (%)	39	36-48
Mean Corpuscular Volume (MCV) (fL)	90	80-100
White blood cell count (/µL)	9020	4000-11000
Neutrophils (N) (%)	73.7	40-70
Lymphocytes (L) (%)	20.7	20-40
Platelets (/µL)	241,000	150,000-450,000
Cholesterol (mg/dL)	123	<200
Triglycerides (TGL) (mg/dL)	55	<150
HDL-C (mg/dL)	45	>50
LDL-C (mg/dL)	67	<100
VLDL-C (mg/dL)	11	2-30
Fasting blood sugar (mg/dL)	84	70-100
Postprandial blood sugar (mg/dL)	128	<140
HbA1c (%)	5.6	<5.7
Urea (mg/dL)	19	15-40
Creatinine (mg/dL)	0.8	0.6-1.1
Total bilirubin (mg/dL)	0.62	0.5-1.0
AST (IU/L)	30	<31
ALT (IU/L)	20	<34
ALP (IU/L)	97	30-120
Total protein (g/dL)	7.3	6.6-8.3
Albumin (g/dL)	3.6	3.5-5.2
Sodium (Na) (mg/dL)	139	135-145
Potassium (K) (mg/dL)	4.3	3.5-5.0
Chloride (Cl) (mg/dL)	99	96-106
Bicarbonate (HCO3) (mg/dL)	30	22-29
Calcium (Ca) (mg/dL)	6.6	8.5-10.5
Phosphorus (PO4) (mg/dL)	6.8	2.5-4.5
Magnesium (Mg) (mg/dL)	1.6	1.7-2.4
TSH (µIU/mL)	5.69	0.4-4
Free T3 (pg/mL)	2.58	2.5-3.9
Free T4 (ng/dL)	1.00	0.58-1.64
Vitamin D3 (ng/mL)	28.12	30-100
Parathormone (pg/mL)	4.28	10-65

[Table/Fig-7]: Shows laboratory tests of case 2 with reference ranges.
HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein cholesterol; HbA1c: Glycosylated haemoglobin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TSH: Thyroid stimulating hormone



[Table/Fig-8]: ECG of the patient showing sinus rhythm along with prolonged QT/QTcBz of 506/505 ms suggestive of hypocalcaemia.

The patient was diagnosed with Fahr's syndrome secondary to hypoparathyroidism and was managed with intravenous calcium gluconate and antiepileptics. She was discharged with oral calcium and vitamin D3 supplements. Upon review after two months, the patient had no further episodes of seizure activity.



[Table/Fig-9,10]: CT scan of the brain in axial sections showing bilateral symmetrical calcifications mainly in the putamen and globus pallidus (red arrows) and bilateral linear symmetrical calcifications in the cerebellum (red arrows), respectively. (Images from left to right)

DISCUSSION

Fahr's disease is a rare, genetically heterogeneous neurodegenerative disorder that typically presents in the fourth to sixth decades of life. It is characterised by abnormal deposits of calcium and other minerals in various brain regions, particularly the basal ganglia, thalamus, cerebellum, and cerebral cortex. Diagnosing Fahr's disease requires the presence of bilateral striopallidodentate calcification on neuroimaging, along with increasing cognitive deterioration and mobility problems that cannot be attributed to biochemical, viral, toxic, or traumatic causes [1].

Fahr's syndrome generally presents in the third and fourth decades and is associated with endocrinopathies, infections like rubella, toxoplasmosis, and brucellosis, or diseases such as Kenny-Caffey syndrome, type 1 neuroferritinopathy, and tuberous sclerosis complex. Fahr's syndrome is most frequently linked to hypoparathyroidism and is potentially amenable to treatment. Therefore, distinguishing between the two entities is crucial for accurate diagnosis and appropriate treatment. Although it most often appears in adulthood, instances may arise during childhood, presenting diagnostic challenges due to its variability and overlapping symptoms with other more common neurodegenerative conditions. Other congenital disorders, such as Cockayne syndrome and tuberous sclerosis, must also be excluded, as they involve calcifications in the brain [2].

Fahr's disease can manifest as movement disorders, including chorea, dystonia, ataxia, and Parkinsonism. Psychiatric manifestations can range from mood disorders and psychosis to cognitive impairment and dementia [3]. Symptoms may mimic those of other neurodegenerative disorders, such as Parkinsonism, often complicating the diagnosis [4]. Neuroimaging plays an important role in diagnosing Fahr's disease by demonstrating bilateral brain calcifications [4].

Recent advancements in genetic studies have identified mutations in several genes, including SLC20A2, PDGFB, PDGFRB, and XPR1, which are linked to familial cases. These genes are implicated in the metabolism of phosphate and calcium, as well as vascular integrity, suggesting that impaired phosphate and calcium homeostasis and vascular dysfunction play critical roles in the pathogenesis of brain calcifications. However, the precise pathophysiological mechanisms remain poorly understood, highlighting the complexity of the disease. These calcifications primarily affect areas involved in motor and cognitive functions, resulting in the varied clinical symptoms observed in Fahr's disease [5]. Early diagnosis and intervention are required to improve long-term outcomes for patients with this disease by slowing disease progression and enhancing the quality of life for affected individuals [6].

Management of Fahr's disease focuses on symptomatic relief, given the lack of curative therapies [2]. Some patients may remain stable for many years with minimal progression, while others may experience a rapid decline in cognitive and motor functions. Hence, periodic assessments are essential for adjusting treatment and identifying disease progression. Addressing co-morbid conditions, such as diabetes mellitus, is also critical, as metabolic disturbances can exacerbate the neurological symptoms of Fahr's disease. Therefore, a multidisciplinary approach involving neurologists, psychiatrists, and other specialists is essential for the optimal management of Fahr's disease [5].

Research is ongoing into novel treatment strategies, including gene therapy and calcium metabolism modulation, but these remain experimental. In a case report by Nimodia D et al., a 20-year-old male patient presented with seizures and severe headaches, with a CT scan of the brain revealing bilateral calcifications in the corona radiata, centrum semiovale, gangliocapsular region, thalamus, and dentate nucleus. The patient had no family history of brain calcifications, and genetic testing was not performed, but he was diagnosed with Fahr's disease after ruling out alternative causes for secondary intracranial calcifications and was treated with antiepileptics [7].

Another case report by Supit VD et al., described a 35-year-old female patient who experienced recurrent seizures, along with psychiatric and behavioural changes [8]. She had a history of thyroidectomy seven years ago and presented with hypocalcaemia and a low PTH level. She was diagnosed with Fahr syndrome and treated with antiepileptics, calcium, and vitamin D supplements, leading to no recurrence of symptoms. A case report by Sapkota D et al., detailed a 61-year-old diabetic female with a history of dementia who presented with complaints of movement and speech difficulties, including dysarthria, tremors, and ataxia [9]. She was diagnosed with Fahr's disease based on CT findings, without genetic analysis, and was treated with levodopa-carbidopa, resulting in significant improvement in her symptoms.

CONCLUSION(S)

The symptoms of Fahr's disease can vary significantly and pose challenges in diagnosis. A comprehensive evaluation, including neuroimaging and, where feasible, genetic testing, is essential to differentiate between Fahr's disease and Fahr's syndrome. The management of Fahr's disease involves a multidisciplinary approach, incorporating neurologists, geneticists, psychiatrists, and rehabilitation specialists to provide symptomatic relief and improve patient outcomes. Current therapeutic options focus on symptomatic treatment, but ongoing research into genetic therapies and calcium metabolism modulation offers hope for the future.

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