

## Case Series

# Clinical and radiological features of Fahr's disease: a mimicker of varied neurological manifestations

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## ABSTRACT

Fahr's disease is a disorder characterized clinically by a wide spectrum of varied clinical-neurological and psychiatric manifestations occurring secondary to intracranial calcifications with subsequent neuronal cell loss. Though the disease can present in early childhood or adolescence the usual age of manifestation is around 4<sup>th</sup>-5<sup>th</sup> decades of life. We report a series of 6 Fahr's disease cases with respect to different clinical and radiological manifestations. The details of different clinical manifestations with respect to the disease were studied. The frequency of symptoms, the radiological pattern of intracranial calcifications and the association of different parameters were studied. Progressive cognitive decline and Parkinsonism was detected in all the patients but in none of them it was the chief presenting feature. Seizure was presenting symptoms in 3 patients. Chorea was encountered in 2 patients as the presenting complaint. Mild wide-based cerebellar ataxic gait was found in only one patient but other cerebellar signs were absent. Athetosis, dyskinesia, or dystonia was present in none of our patient. CT scan revealed symmetric basal nuclei and cerebellar calcification in all patients. The disease needs a high index of suspicion and CT brain scanning should always be performed in patients younger than 50 years who present with refractory seizures, Parkinsonism and cognitive decline. However radiological findings did not predict the presentation and outcome.

**Keywords:** Computerized tomography, Fahr's disease, Intracranial calcifications, Parkinsonism

## INTRODUCTION

Fahr's syndrome is an autosomal dominant neurodegenerative disorder characterized clinically by an array of varied clinical-neurological and psychiatric manifestations occurring secondary to intracranial calcifications with subsequent neuronal cell loss. Fahr's disease or idiopathic striopallidodentate calcinosis is the presence of bilateral symmetrical intracranial calcifications in the basal nuclei, thalamus, dentate nucleus, and centrum semiovale regions are due to unknown etiology.<sup>1,2</sup> Though the disease can present in early childhood or adolescence the usual age of manifestation is around 4<sup>th</sup>-5<sup>th</sup> decades of life. The

disease may present as a variable combination of involuntary movements (chorea, athetosis, dyskinesia, and dystonia) and Parkinsonism; seizures, progressive cognitive decline, and cerebellar dysfunction.<sup>1</sup>

Our study aims at describing different clinical and radiological presentations in the case series analyzing demographic and radiological features predicting the clinical outcome and presentations. Authors performed a retrospective observational case series study conducted at the department of pediatrics and medicine with prior ethical approval for the same. Clinical and radiological details were retrieved from hospital database cases diagnosed with Fahr's disease. Six different individuals

(n=6) who visited our hospital in the recent past diagnosed with Fahr's disease were studied in detail for clinical and radiological findings.

All the patients underwent a thorough medical and neurological examination. All of them had routine blood testing, including serum calcium, serum phosphate, serum alkaline phosphatase, serum vitamin D, and serum parathyroid hormone and non-contrast CT brain scanning were done at the time of diagnosis.

The diagnosis of Fahr's disease was made depending on the finding of normal serum calcium and phosphate and the extensive symmetrical calcification on the background of a variable combination of involuntary movements, Parkinsonism, seizures, cognitive decline, and cerebellar dysfunction. Detailed case characteristics follow.

## CASE SERIES

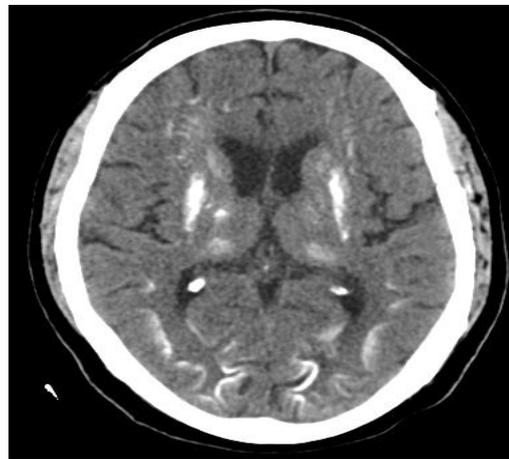
### Case 1

A 12 year old female child was brought by her parents to our pediatrics outpatients' clinic. For the last 3 years, they have noticed that the child was irritable with multiple episodes of intractable seizures and deteriorating academic performance. She had normal childhood developmental milestones and had no known chronic illnesses. She was taking two anticonvulsants for seizures for the last three years. She has 1 brother and 1 sister; both of them were healthy. She had no family history of epilepsy. The overall first impression was a "seizure disorder." However, she showed apathy, mental slowness, and prominent impairment in abstract thinking. She had no rigidity, hypokinesia or tremor. Neither chorea nor dystonia was found. Both planter reflexes were flexors. Her brain CT scan revealed extensive bilateral basal ganglia, deep white matter calcifications which appear symmetric but there were no cerebellar calcifications as in Figure 1 and 2. Final diagnosis of Fahr's disease was made and the family was informed about the disease and its possible outcomes. The patient was put on valproate 40mg/kg/day and levetiracetam 20mg/kg/day. After 12 months of follow-up, her cognitive dysfunction was more or less the same and neither seizures nor involuntary movements were noted.

### Case 2

A 46 years old male presented with generalized seizures for the preceding 8 weeks. He had noticed a progressive memory impairment and poor social interaction. The patient resides in a rural area, was illiterate, and works in a local grocery store. The patient was non-alcoholic and there was no history of head trauma or chronic illness. On further questioning, the family stated that the patient always tried to avoid attending family events, shows easy forgetfulness, and was angry most of the time. All the siblings were healthy. Neurological examination revealed

poor abstract thinking, mental slowness, and easy irritability and distraction. Recent memory testing was grossly impaired, but the immediate recall and remote memory were intact. His deep tendon reflexes were normal and symmetrical with flexor plantar reflexes. He had generalized rigidity, hypokinesia, and mild bilateral resting tremor. His blood tests were within their normal reference range and his CT brain scan is showed extensive bilateral basal ganglia, centrum semiovale calcifications. It was diagnosed as Fahr's disease and the family members were informed about the possible course of the disease. Electroencephalography revealed generalized epileptiform discharges. Increasing the doses of oral carbamazepine rendered him seizure-free. No further seizures developed over 1 year of follow-up and no involuntary movements were noted. He currently takes oral carbamazepine (1200mg/day), donepezil (10mg/day) and sertraline (100mg/day). His cognitive impairment has been more or less stabilized.

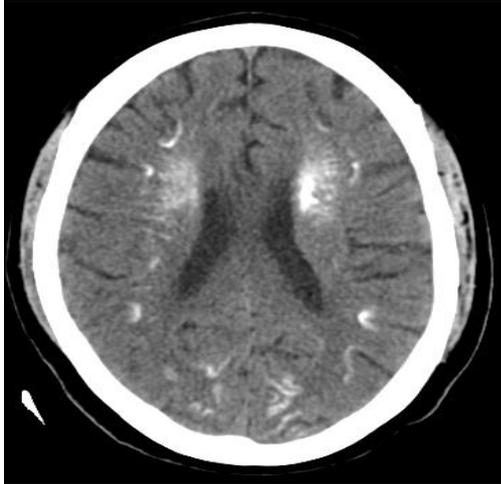


**Figure 1: Non-contrast CT brain scan of a 46 year old male who had cognitive and psychiatric symptoms due to Fahr's disease. Note that the basal ganglia, adjacent thalami, subcortical hemispheric white matter are calcified.**

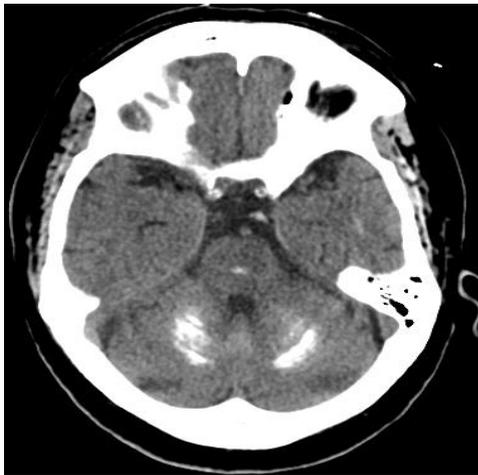
### Case 3

An 18 years old female had been experiencing progressively worsening generalized chorea for the last 2 years. Before this, the patient was completely healthy. The patient had no chronic illnesses and there was no history of seizures. They reside in a village. She had 2 healthy brothers but father had a history of progressive memory impairment and seizures beginning at 55 years of age to which he succumbed and not investigated or treated. Their local GP diagnosed her with post-streptococcal Sydenham's chorea 2 years ago and she had been receiving oral diazepam (5mg/day) since then. Examination reveals gross impairment in recent memory (with intact immediate recall and remote memory), prominent apathy, mental slowness, generalized rigidity, hypokinesia, and moderate bilateral resting tremor. The choreic movements asymmetrically involving both upper

and lower limbs and she demonstrated dysarthria. Her deep tendon and plantar reflexes were normal. Diagnostic workout was unremarkable except for bilateral symmetrical intracranial calcification (Figure 3 and 4). Accordingly, Fahr's disease was labeled and oral clonazepam (4mg/day) and valproic acid (1000mg/day) were advised on which patient improved but not abolished her chorea over a follow-up period of 13 months.



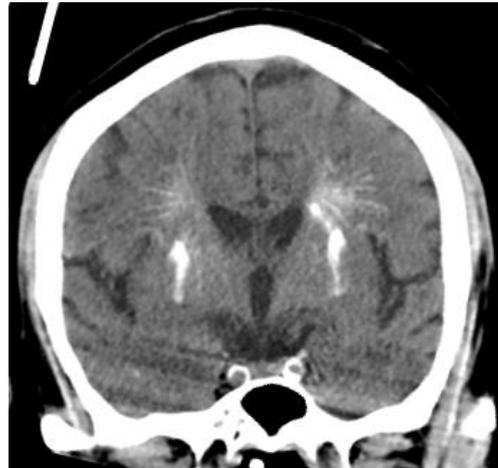
**Figure 2. Non-contrast CT brain scan of a 12 year old female who had generalized seizure for 2 years. Her diagnosis turned out to be Fahr's disease. Note the wide-spread and symmetrical intracerebral calcification of subcortical and periventricular white matter.**



**Figure 3. Non-contrast CT brain scan of a 22 year old male who had chorea, ataxia, parkinsonism and cognitive decline for 3 years. Her diagnosis turned out to be Fahr's disease. Note the wide-spread and symmetrical cerebellar calcifications.**

Clinical presentations of Case no 4,5 and 6 are discussed in Table 1. These patients were diagnosed and treatment started but subsequently lost to follow up. All three

patients had no previous history of chronic ailments and no similar family history.



**Figure 4. Non-contrast CT brain scan of a 16 year old female who had rigidity and hypokinesia. Her diagnosis turned out to be Fahr's disease. Note the wide-spread and symmetrical intracerebral calcification at the basal ganglia, thalami, and subcortical white matter of the hemispheres.**

There were 3 females in their 2<sup>nd</sup> decade of life while two males in their 5<sup>th</sup> decade and one in the 3<sup>rd</sup> decade. All the patients were from rural areas. Progressive cognitive decline was detected in all the patients, and in one of them, it was the core presenting complaint. Parkinsonism was found at the time of diagnosis in all patients but in none of them, it was the chief presenting feature. Seizures developed in three patients, no seizures developed in the other 3 patients during the whole period of follow-up. Chorea was encountered in 2 patients as the presenting complaint. Mild wide-based cerebellar ataxic gait was found in only one patient but other cerebellar signs were absent. Athetosis, dyskinesia, or dystonia was present in none of our patient. All of them required prolonged symptomatic treatment. Three of them were followed up for one year but three lost to follow up within two months of diagnosis and treatment.

## DISCUSSION

The exact prevalence of Fahr's disease is not known but yet intracranial calcifications can be detected incidentally in up to 0.3-1.2% of NCCT examinations of the brain.<sup>3</sup> Although bilateral and symmetric basal ganglia calcification is known to be associated with multiple medical conditions, the exact etiology of Fahr's disease is still unknown.<sup>4</sup> Genetic alterations have been attributed to chromosome 14q48.<sup>5</sup> The late German pathologist, Karl Fahr published a paper in the year 1930 describing an extensive intracerebral calcification without an obvious cause in an elderly patient.<sup>6</sup> His name has been linked to this observation since then. Predominant radiological pattern being basal ganglia calcification. The diseases that have been described with diffuse bilateral

symmetric striopallidodentate calcification are primary hypoparathyroidism, lupus, tuberous sclerosis, Alzheimer’s disease, myotonic muscular dystrophy and mitochondrial encephalopathies.<sup>7-9</sup> When authors can’t

attribute the cause for striopallidodentate calcinosis with any of the above disease the condition it is termed as Fahr’s disease.

**Table 1: Patients’ demographic and clinical features of case 4 to 6.**

Age	Gender	Involuntary movements	Parkinsonism	Seizures	Cognitive impairment	Cerebellar dysfunction
16	F	No	Rigidity, hypokinesia, no tremor	No	Yes	No
50	M	No	Rigidity, hypokinesia, mild bilateral resting tremor	Yes	Yes	No
22	M	Chorea	Rigidity, hypokinesia, moderate bilateral resting tremor	No	Yes	Ataxic gait

Fahr’s disease, which can be sporadic or familial, demonstrates no abnormalities in calcium metabolism and kinetics. Martinelli and colleagues suggested an autosomal dominant inheritance of vitamin D metabolism while Sly and coworkers found an autosomal recessive deficiency of carbonic anhydrase II in red blood cells.<sup>10,11</sup> Geschwind and colleagues found that a genetic abnormality at chromosome 14q48 is the culprit behind the development of Fahr’s disease while Manyam disagrees and states that calcium and other mineral deposits inside the brain of Fahr’s patients cannot be linked to a single chromosomal locus.<sup>12,13</sup> However, recently, Hsu et al discovered that a mutation in the gene SLC20A2 accounts for as many as 41% of familial Fahr’s disease.<sup>14</sup>

The true incidence of the disease is unknown. Verulashvili and colleagues concluded that 0.3 to 1.5% of the CT scan in general population harbor “physiological” intra-cerebral calcification, which is entirely asymptomatic and is detected because of the widespread use of CT scanning for other indications.<sup>15</sup> The incidence of intracranial calcification increases with advancement of age because of ferruginization and calcium deposition in the capillaries of the basal ganglia. Therefore, the occurrence of intracranial calcification in young individuals should always be taken seriously.<sup>16</sup> According to Manyam and coworkers, CT brain scanning is the preferred imaging modality in the detection of intracerebral calcification.<sup>17</sup> Radiological evidence of bilateral basal ganglia calcification together with neuropsychiatric or extrapyramidal manifestations on the background of normal calcium and phosphate metabolism the diagnosis of Fahr’s disease can be made confidently. Other researchers mandate the occurrence of seizures, rigidity, and cognitive decline with bilateral basal ganglia calcification.<sup>18</sup>

In the present study, male to female ratio is 1:1 and Parkinsonism is present in all except one. According to Manyam and colleagues, men are affected more than

women and that movement disorders account for 55% of the total symptomatic patients.<sup>19</sup> In his study population movement disorders, like Parkinsonism 57%, chorea 19%, tremor 8%, dystonia 8%, athetosis 5%, and orofacial dyskinesia 3% seen. Cognitive decline is present in all the patients in the present study.

Cognitive decline is the second most common manifestation, followed by cerebellar dysfunction and speech disorders.<sup>18</sup> The cognitive decline in these patients are consistent with a subcortical pattern of dementia. The majority of Fahr’s disease patients demonstrate a constellation symptoms like easy forgetfulness, irritability, slowness of thought processes, mild intellectual impairment, apathy, depression, and inability to manipulate knowledge; which in combination points towards frontal lobe dysfunction.<sup>16,20,21</sup> The memory impairment is marked by a prominent deficit of spontaneous recall, rather than problems of encoding and storage of new materials that are pathognomic of the cortical dementias.<sup>16,22</sup> In the present study, generalized tonic-clonic seizures were present in 4 out of 6 patients. Hoque et al in 2010 reported a case of Fahr’s disease presenting as complex partial seizures with secondary generalization and associated behavioral abnormalities while Ashtari and Fatehi reported atonic seizures in Fahr’s disease.<sup>23,24</sup>

Patients 3 and 6 came to medical attention because of the history of worsening generalized chorea. Patient 3 was misdiagnosed with Sydenham’s chorea. Abubakar reported on a middle-aged woman who presented with a 3-week history of left-sided hemichorea, which was ascribed to an “ischemic stroke” but her diagnosis was Fahr’s disease.<sup>18</sup> Although involuntary movements are the commonest component of Fahr’s disease, chorea constitutes less than 20% of them. The list of causes of “secondary” bilateral basal ganglia calcification is long and encompasses a multitude of genetic, developmental, metabolic, toxic, inflammatory, and infectious etiologies. Therefore, different ages and genders are targeted. However, in case of Fahr’s disease, the intracerebral

calcium deposition starts in the 3rd decade and may take around 20 years to create its clinical manifestation, keeping it in mind that at least one-third of the affected individuals never become symptomatic in their lifetime.<sup>7,13,17</sup>

The treatment is principally symptomatic and is targeted towards the complaints to improve the quality of life. Prior therapeutic attempt to improve the disease course was done by Skvortsov and colleagues in 1987 with use of xydifon, deferoxamine, penicillamine, combined with antioxidants, calcium antagonists and drugs improving brain microcirculation produced a positive effect in the course of the disease.<sup>25</sup>

Limitations of this study include a smaller sample size given the rarity of the disease. Due to the retrospective nature of the study, the period of follow-up could not be extended we only reported the available follow up a record of 50% patients which was relatively short to allow us to observe the symptomatology and uncover other manifestations of the disease, as the disease is progressive. There are no similar previously reported cases from our region to compare our results with.

## CONCLUSION

All our patients were from rural areas with poor health care assess and were misdiagnosed as other neurological diseases for long periods before presenting to us. Their presentations comprised a wide array of uncommon neurological manifestations like Parkinsonism and cognitive decline. The disease is infact a mimicker needs a high index of suspicion and CT scanning of brain should always be performed in patients younger than 50 years who present with Parkinsonism, cognitive decline and/or unexplained refractory seizures. However, the pattern of intracranial calcifications in CT scans did not predict the presentation, its severity or outcome.

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