



Fahr's Disease: A Case Series

Fahr Hastalığı: Bir Olgu Serisi

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ABSTRACT

Fahr's disease is a rare idiopathic bilateral and symmetrical calcification of the basal ganglia, thalami, subcortical hemispheric white matter, and deep cerebellar nuclei that usually presents between the 4th and 6th decade of life with a variable combination of involuntary movements, Parkinsonism, presenile subcortical dementia, seizures, and ataxia. This longitudinal observational case series was conducted at the neurology outpatients' department of Sulaimaniya general teaching hospital, Iraq. Three patients were diagnosed with Fahr's disease. Their chief presenting complaint and other coexistent clinical features were noted and followed-up for at least one year. The ages of those consecutive patients were 25, 34, and 21 years, respectively. Two were females and the other patient was a male. The chief presenting complaint among the 3 patients was heterogeneous; cognitive impairment, seizures, and chorea, respectively. At the time of diagnosis, Parkinsonism and cognitive decline were present in all patients. The 3 patients never developed dystonia, dyskinesia, or athetosis and one patient only had mild cerebellar ataxia. Seizures were the presenting feature in one patient and they never developed in the other 2 patients. All patients had a variable degree of intracerebral calcification. Fahr's disease has heterogeneous phenotypes and the brain radiological findings do not predict the clinical presentation and course. Although Parkinsonism was not the presenting feature, it was found in all patients at the time of diagnosis. Involuntary movements and cerebellar dysfunction were uncommon and the cognitive impairment was of the frontal lobe subcortical dysfunction.

Key Words: Fahr's disease, striatopallidodentate calcinosis, seizures, involuntary movements, cognitive decline.

ÖZET

Fahr hastalığı, bazal ganglion, talamus, subkortikal hemisferik beyaz cevher ve derin serebellar nukleusda bilateral ve simetrik olarak kalsiyum birikmesiyle karakterize nadir görülen, idiopatik bir hastalıktır. Genellikle yaşamın 4. ve 6. dekatlarında ortaya çıkar. İstemsiz hareketler, Parkinsonizm, presenil subkortikal demans, nöbet ve ataksi gibi bulgularla birlikte değişik kombinasyonlar şeklinde görülebilir. Bu longitudinal gözlemsel vaka serisi Irak Süleymaniye Eğitim Hastanesi Nöroloji bölümünde yapılmıştır. Üç hastada Fahr hastalığı teşhis edildi. Olguların esas şikayetleri ve bunlara eşlik eden diğer klinik özellikleri not edilerek en az bir yıl takip edildi. Hastaların yaşları sırasıyla 25, 34 ve 21'dir. İki kadın, biri ise erkektir. Bu üç hastanın esas şikayetleri heterojendir ve sırasıyla kognitif bozukluk, nöbet ve korea şeklindedir. Tanı koyarken tüm hastalarda kognitif gerileme ve parkinsonizm bulguları mevcuttu. Üç hastada da distoni, diskinezi veya atetozis asla gelişmedi, sadece bir hastada hafif şiddette serebellar ataksi görüldü. Nöbet sadece bir hastada görülürken diğer iki hastada gelişmedi. Tüm hastalarda değişen derecelerde intraserebral kalsifikasyon vardı. Fahr hastalığı radyolojik ve fenotipik bulguları heterojenite gösteren, klinik özellikleri tahmin edilemeyen bir hastalıktır. Bu hastalığın parkinsonizm özelliği olmasada tüm hastalarda teşhis sırasında parkinsonizm bulguları olmaktadır. İstemsiz hareketler ve serebellar disfonksiyon yaygın değildir, ve kognitif bozukluk ile frontal lob subkortikal disfonksiyonu vardır.

Anahtar Kelimeler: Fahr hastalığı, striatopallidodentat kalsinozis, nöbet, istemsiz hareket, kognitif gerileme.

INTRODUCTION

Fahr's disease refers to the idiopathic development of bilateral and symmetrical calcification of the basal ganglia, thalami, hemispheric subcortical white matter (particularly centrum semiovale), and deep cerebellar nuclei (especially the dentate ones). The disease encompasses a variable combination of involuntary movements (chorea, athetosis, dyskinesia, and dystonia) and Parkinsonism; seizures, progressive cognitive decline, and cerebellar dysfunction are additional features in some, but not all, patients¹.

Patients and their presentation

This longitudinal observational case series study was conducted at the neurology outpatients' department of Sulaimaniya general teaching hospital. Three different individuals who visited our outpatients' clinic were diagnosed with Fahr's disease and were followed-up for at least one year.

All patients (n=3) underwent a thorough medical and neurological examination by a single neurologist. All of them underwent routine blood testing, including serum calcium, serum phosphate, serum alkaline phosphatase, serum vitamin D, and serum parathyroid hormone. A 12-lead resting ECG, electroencephalography, and non-contrast CT brain scanning were done at the time of diagnosis. None of the patient underwent brain MRI examination or a CSF analysis.

The diagnosis of Fahr's disease was made depending on the constellation of normal serum calcium and phosphate and the wide-spread symmetrical intracerebral calcification on the background of a variable combination of

involuntary movements, Parkinsonism, seizures, cognitive decline, and cerebellar dysfunction.

Patient 1

A 25-year-old single female was brought by her parents to our neurology outpatients' clinic. Over the preceding 6 years, they have noticed a progressive impairment in short-term memory, poor sleep, and social isolation. She was irritable, feeling unhappy all the time, and pessimistic. They live in a village, near the Iraq-Iran border which lacks medical services. She demonstrated normal childhood developmental milestones and had no chronic illnesses. She was not taking any form of medications. The mother denied the occurrence of seizures or involuntary movements. She has 3 brothers and 4 sisters; all of them are healthy. The overall first impression was a "depressive disorder not otherwise specified." She was illiterate; therefore, several aspects of her minimal status examination were ignored. However, she demonstrated apathy, mental slowness, and prominent impairment in abstract thinking. She had generalized rigidity and hypokinesia but no tremor. Neither chorea nor dystonia were found. Both planter reflexes were flexors. Her brain CT scan is shown in figure 1. A diagnosis of Fahr's disease was made accordingly and the family was educated about the disease and its possible course. Daily oral rivastigmine (3 mg/day) and sertraline (100 mg/d) were prescribed and alprazolam (0.5 mg/d) was used infrequently for her irritability and to help her sleep. After 18 months of follow-up, her cognitive dysfunction was more or less the same and neither seizures nor involuntary movements were noted.

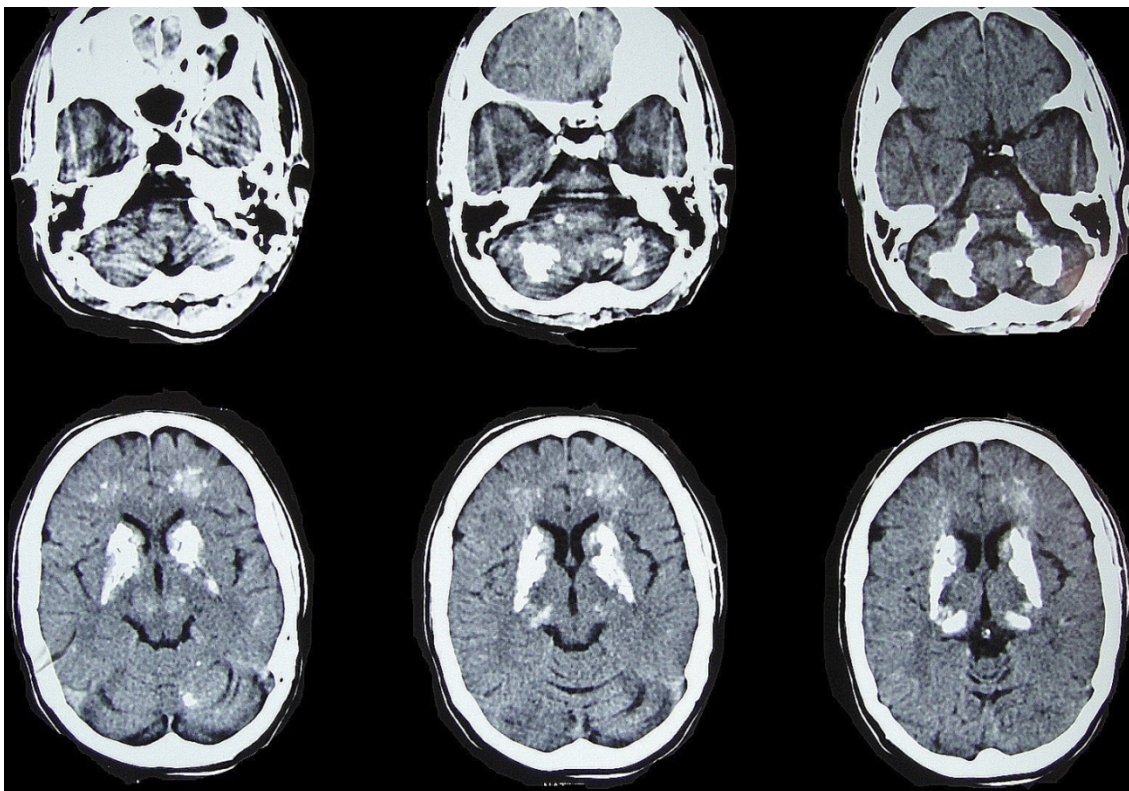


Figure 1. Non-contrast CT brain scan of a 25-year-old female with Fahr's disease who presented with frontal lobe-like cognitive dysfunction. The calcification is bilateral and symmetrical and involves the basal ganglia, thalami, subcortical white matter, and dentate cerebellar nuclei.

Patient 2

A 34-year-old single male experienced 3 generalized seizures over the preceding 2 weeks. His older brother said that the patient had "depression" for which their local GP had prescribed oral fluoxetine (40 mg per day) 2 months ago, after noticing a progressive memory impairment and poor social interaction. The patient resides in a rural area, is illiterate, and works in a local grocery store. The patient denied ingesting illicit drugs, and there was no history of head trauma. On careful questioning, the family stated that patient always tries to avoid attending family events, shows easy forgetfulness, and is angry most of time. He has 5 brothers and 2 sisters; all of them are healthy. Examination reveals 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. There was no agnosia. His deep tendon reflexes were normal and symmetrical with flexor planter reflexes. He has generalized rigidity, hypokinesia, and mild bilateral resting tremor. His blood tests were within their normal reference range and his CT brain scan is shown in figure 2. A diagnosis is of Fahr's disease was then made and the family was informed about the possible course of the disease. Electroencephalography revealed generalized epileptiform discharges. Escalating doses of oral carbamazepine rendered him seizure-free. No further seizures developed over a 1 year period of follow-up and no involuntary movements were

noted. He currently takes oral carbamazepine (1200 mg per day), sertraline (100 mg per day),

and (donepezil 10 mg per day). His cognitive impairment has been more or less stabilized.



Figure 2. Non-contrast CT brain scan of a 34-year-old male who had recurrent seizures due to Fahr's disease. Note that the basal ganglia, adjacent thalami, subcortical hemispheric white matter are calcified.

Patient 3

A 21-year-old single female had been experiencing progressively worsening generalized choreic movements for the last 2 years. Until 2 years ago, the patient was completely healthy, as the mother had stated. Their family history is unremarkable and the patient has no chronic illnesses. There was no history of seizures. They reside in a village outside Sulaimaniya city. She has 2 healthy brothers. Their local GP diagnosed her with post-streptococcal Sydenham's chorea 2

years ago and she had been receiving oral diazepam (5 mg per 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 involve both upper and lower limbs and she demonstrates hyperkinetic dysarthria. Her deep tendon and planter reflexes were normal. Her work-up was unremarkable apart from bilateral symmetrical intracerebral calcification (figure 3).

Accordingly, Fahr's disease was labeled as the culprit and oral clonazepam (4 mg per day) and valproic acid (1000 mg per day) improved but not

abolished her chorea over a follow-up-period of 13 months. No convulsions, dyskinesia, or dystonia had developed during the aforementioned period.

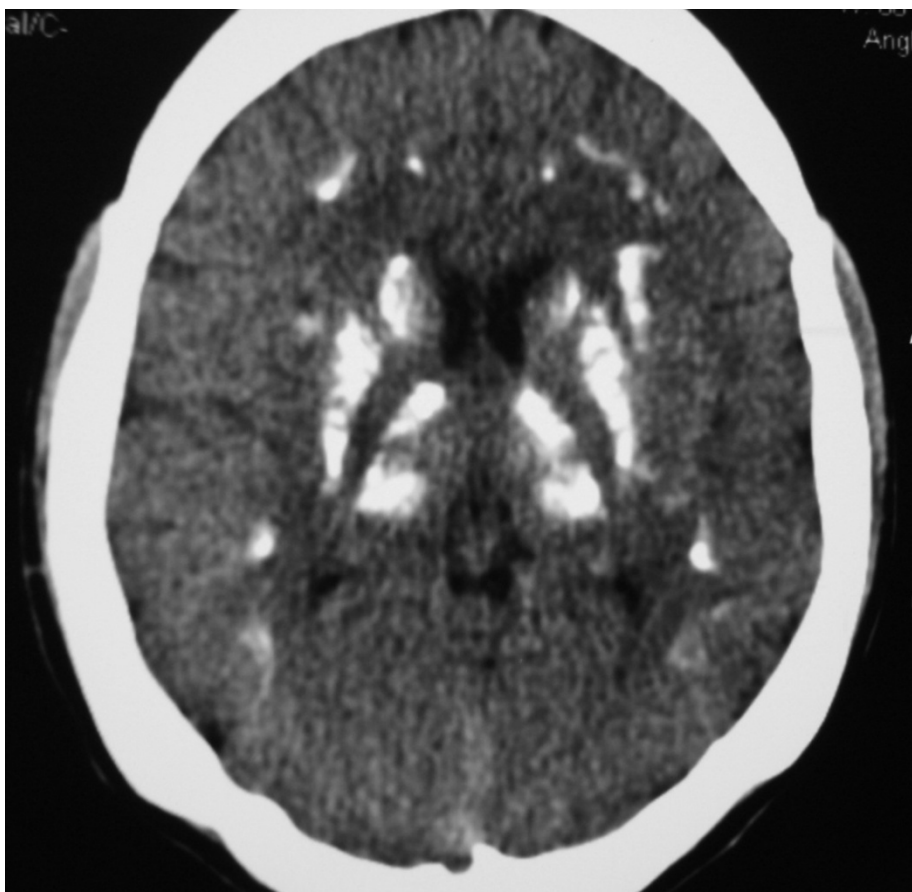


Figure 3. Non-contrast CT brain scan of a 21-year-old female who had generalized chorea for 2 years. Her diagnosis turned out to be Fahr's disease. Note the wide-spread and symmetrical intracerebral calcification at the basal ganglia, thalami, and subcortical white matter of the hemispheres.

Table 1. Patients' characteristics and their clinical features. Those patients were enrolled consecutively.

No.	Age	Gender	Height and Weight	Involuntary Movements*§	Parkinsonism*	Seizures*	Cognitive Impairment*	Cerebellar Dysfunction*
1	25	F	152 cm, 59 Kg	No	Rigidity, hypokinesia, no tremor	No	Yes¶	No
2	34	M	168 cm, 74 Kg	No	Rigidity, hypokinesia, mild bilateral resting tremor	Yes¶	Yes	No
3	21	F	161 cm, 63 Kg	Chorea¶	Rigidity, hypokinesia, moderate bilateral resting tremor	No	Yes	Ataxic gait

*At the time of diagnosis;. ¶ Main presenting complaint; § Chorea, dystonia, dyskinesia, and/or athetosis.

RESULTS

Table 1 displays the various patients' characteristics and their clinical presentation. There were 2 females in their 3rd decade of life while the 3rd patient was a male in his 4th decade. All of them were single. The 2 females were non-employed but the male worked in a local grocery store. All patients resided in rural areas within the governorate of Sulaimaniya, but far away from Sulaimaniya city, where the only tertiary neurology center lies in.

Parkinsonism was found at the time of diagnosis in all patients but in none of them it was the chief presenting feature. Progressive cognitive decline was detected in all patients, and in one of them, it was the core presenting complaint. Seizures developed in one patient, which called for neurological advice; no seizures developed in the other 2 patients during the whole period of follow-up. Of all involuntary movements characteristic of Fahr's disease, only chorea was encountered and it was found in 1 patient only as the presenting complaint. Mild wide-based cerebellar ataxic gait was found in one patient; other cerebellar signs were absent. None of the patients presented with, or later on developed, athetosis, dyskinesia, or dystonia.

DISCUSSION

The late German pathologist, Karl Fahr, published a paper² in the year 1930 describing an extensive intracerebral calcification without an obvious cause in an elderly patient. His name has been linked to this observation since then, although idiopathic, widespread, and bilateral intracerebral calcification has long been noted and reported before the publication of Fahr's paper.

In this disease, calcium deposition is bilateral and symmetrical and involves predominantly the basal ganglia, thalami, hemispheric subcortical white matter (particularly centrum semiovale), and deep cerebellar nuclei (mainly the dentate ones)¹. Therefore, labeling the disease as striatopallidodentate calcinosis (SPDC) is more

appropriate than Fahr's disease, which is a misnomer. According to Manyam³ there are 35 additional names used in the literature for the same condition!

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^{4,5}. Geschwind and colleagues⁶ found that a genetic abnormality at chromosome 14q48 is the culprit behind the development of Fahr's disease while Manyam³ disagrees and states that calcium and other mineral deposits inside the brains of Fahr's patients cannot be linked to a single chromosomal locus. However, recently, Hsu et al⁷ discovered that a mutation in the gene SLC20A2 accounts for as many as 41% of familial Fahr's disease.

The true incidence of the disease is unknown. Verulashvili and colleagues⁸ concluded that 0.3 to 1.5% of the general population harbor "physiological" intra-cerebral calcification, which is entirely asymptomatic and is detected because of the widespread use of CT brain scanning. The incidence of this calcification increases with age because of ferruginization and calcification of the capillaries of the basal ganglia. Therefore, the occurrence of intracranial calcification in young individuals should always be taken seriously¹. According to Manyam and coworkers, CT brain scanning is the preferred imaging modality in the detection of intracerebral calcification⁹.

The diagnosis of Fahr's disease requires the presence of a brain imaging evidence of bilateral basal ganglia calcification together with neuropsychiatric and/or extrapyramidal manifestations on the background of normal calcium and phosphate metabolism. Other researchers mandate the occurrence of seizures, rigidity, and cognitive decline with bilateral basal ganglia calcification¹⁰.

According to Manyam and colleagues¹¹ men are affected more than women and that movement disorders account for 55% of the total symptomatic patients. Of the movement disorders, Parkinsonism accounted for 57%, chorea 19%, tremor 8%, dystonia 8%, athetosis 5%, and orofacial dyskinesia 3%.

Cognitive decline is the second most common manifestation, followed by cerebellar dysfunction and speech disorders¹⁰. The cognitive decline is consistent with a subcortical type of dementia. The majority of patients demonstrate a constellation of easy forgetfulness, irritability, slowing of thought processes, mild intellectual impairment, apathy, depression, and inability to manipulate knowledge; a combination which points to frontal lobe dysfunction^{1,12,13}. The memory impairment is marked by a prominent deficit of spontaneous recall, rather than problems of encoding and storage of new materials that is pathognomonic of the cortical dementias^{1,14}.

Previously, we reported on patient 1¹ who presented with a frontal lobe-like cognitive dysfunction. The pertinent literature does mention patients who presented solely with presenile type of subcortical dementia and who were eventually given a diagnosis of Fahr's disease^{15,16}.

Patient 2 was initially diagnosed with retarded depression and later on developed generalized tonic-clonic seizures. Hoque and colleagues reported on a Fahr's disease patient who presented with complex partial seizures (with secondary generalization) and behavioral abnormalities¹⁷ while Ashtari and Fatehi^[18] reported on atonic seizures in Fahr's disease. Epilepsy is a rare manifestation of Fahr's disease.

Patient 3 came to medical attention because of a 2-year history of worsening generalized chorea. She was misdiagnosed with Sydenham's chorea. Abubakar^[10] reported on a middle-aged woman who presented with a 3-week history of left-sided hemichorea, which was ascribed to an "ischemic stroke." Her diagnosis was Fahr's disease, actually. Although involuntary movements

are the commonest component of Fahr's disease, chorea constitutes less than 20% of them.

The list of causes³ 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 Fahr's disease, the intracerebral calcium deposition starts in the 3rd decade and may take around 20 years to create its symptomatology, keeping in mind that at least one third of the afflicted individuals never become symptomatic^{1,3,9}.

The treatment is principally symptomatic and is targeted towards the complaints to improve the quality of life. The only reported attempt to improve the disease was that of Skvortsov and colleagues¹⁹. They found that therapy with complexones (xydifon, penicillamine, deferoxamine) combined with antioxidants, calcium antagonists, drugs improving the microcirculation, etc., produced a marked positive effect.

CONCLUSION

Our patients were younger than those reported in the literature and 2 out of the 3 patients were females. All of them were Kurdish (an ethnic minority living at the northeast area of Iraq), single and illiterate, and live in rural areas. Their main presenting feature was different from each other and comprised an uncommon manifestation of the disease. Parkinsonism and cognitive decline were found in all patients while dystonia, dyskinesia, and athetosis were absent in all of them. The radiological findings did not predict the presentation and outcome. 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 Parkinsonism and cognitive decline.

Limitations

1. The number of cases was definitely small, given the rarity of the disease and the

relatively small population of Sulaimaniya governorate of approximately 2000000 populations.

2. The period of follow-up was relatively short to allow us observe the symptomatology and uncover other manifestations of the disease, as the disease is progressive.
3. There are no similar previously reported cases from Iraq to compare our results with.
4. Taking in consideration the aforementioned factors, the results might well have been different if the number of cases was larger, other ethnic groups were involved, and the period of follow-up was longer.

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