

Fahr's Disease and Frontal Lobe-Like Cognitive Dysfunction

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ÖZET:

Fahr hastalığı ve frontal lob benzeri bilişsel işlev bozukluğu

Giriş: İdiyopatik, bilateral ve simetrik striatopallidodentate kalsinozis (veya Fahr hastalığı) genellikle anormal hareketler, parkinsonizm, nöbetler ve bilişsel işlev bozukluğunun gibi belirtilerin değişken birliktelikleri ile yaşamın dördüncü, altıncı ve onuncu yılları arasında nadir görülen bir hastalıktır. Beyin BT görüntülemesinin yaygın kullanımı sebebiyle belirsiz olguların teşhisi giderek artmaktadır.

Olgu sunumu: Biz yaygın beyin içi kalsifikasyon ve normal kalsiyum metabolizmasına sahip; bellek bozukluğu, zihinsel yavaşlık, iritabilite, apati, kötü gece uykusu ve sosyal izolasyon gibi belirtilerin eşlik ettiği 6 yıl içinde giderek artan frontal-lob benzeri bilişsel yıkımla seyreden 25 yaşında bir kadın hastayı sunuyoruz. Hastanın genel bir rijiditesi vardı fakat titremesi yoktu. Bir buçuk yıldan fazla bir süredir devam eden takipleri sırasında hastada nöbet gelişmedi.

Sonuç: Fahr hastalığı karşımıza sadece frontal lob benzeri bilişsel işlev bozukluğu olarak ve beynin radyolojik bulgularının klinik belirtileri ve hastalığın gidişatını öngöremediği bir klinik tablo ile ortaya çıkabilir.

Anahtar sözcükler: Fahr hastalığı, frontal lob, bilişsel işlev bozukluğu, kafa içi kalsifikasyon

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ABSTRACT:

Fahr's disease and frontal lobe-like cognitive dysfunction

Introduction: Idiopathic, bilateral, and symmetric striatopallidodentate calcinosis (or Fahr's disease) is a rare disease that usually presents between the fourth, sixth, and tenth decades of life with a variable combination of abnormal movements, Parkinsonism, seizures, and cognitive dysfunction. Asymptomatic cases are being increasingly recognized because of the widespread use of brain CT scanning.

Case presentation: We report a 25-year-old female who had diffuse intra-cerebral calcification and normal calcium metabolism; her presentation was progressive frontal lobe-like cognitive decline over a period of 6 years; impairment in memory, mental slowness, irritability, apathy, poor night time sleep, and social isolation. She has generalized rigidity but no tremor. Over a period of one and a half year of follow-up, she had not developed seizures.

Conclusion: Fahr's disease may present as an isolated frontal lobe-like cognitive dysfunction and that the radiological findings of brain do not predict the clinical presentation and course.

Key words: Fahr disease, frontal lobe, cognitive dysfunction, intracranial calcification

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BACKGROUND

In 1930, the German pathologist Karl Fahr reported on an adult case of idiopathic and extensive calcification of the basal ganglia (1). Although bilateral and diffuse cerebral calcification was noted long before the publication of Fahr's paper, but his name has been attached to this observation since then (2). Actually, his contribution added little to the knowledge of this condition. In Fahr's disease, calcium deposition occurs bilaterally and symmetrically in the basal ganglia, thalamic, deep cerebellar nuclei, and white matter of the cerebral

hemispheres and most cases present with abnormal movements and Parkinsonism. Seizures, sub-cortical dementia, and cerebellar dysfunction may be additional features in some patients.

CASE PRESENTATION

A 25-year-old single woman was brought to our neurology outpatients' clinic by her parents. The family stated that the patient had been experiencing impairment in memory, irritability, poor night time sleep, and social isolation over the past 6 years, a constellation that points

towards a “depressive disorder not otherwise specified.” She was not receiving any kind of medical treatment. The parents denied any form of involuntary movements or seizures but on careful questioning, the family described their daughter as being anhedonic, pessimistic, self-doubting, duty-bound, and chronically unhappy; a picture that is consistent with a depressive personality. She had a normal childhood development and milestones. Her past history was unremarkable. She has 3 brothers and 4 sisters; all are healthy. The patient was illiterate and did not attend to any school, as the family resides in a small village on the Iraq-Iran border; this illiteracy intersected with several aspects of mental status and language examinations. However, examination revealed prominent apathy and mental slowness as well as impaired abstract thinking. Her remote memory was intact but the immediate recall and recent memory were impaired mildly. Neither abnormality in language function, nor agnosia were found. She demonstrated generalized rigidity but no tremor was detected. Both planter reflexes were flexor. She underwent a battery of lab tests: complete blood counts, ESR, blood film, blood urea and electrolytes, serum AST, ALT, alkaline phosphatase, and serum total bilirubin, random blood sugar, lipid profile, serum T₃, T₄, and TSH; serum VDRL; serum calcium and phosphorus; general urine examination; and serum vitamin B12. All of those turned out to be negative. A non-contrast CT brain scanning revealed extensive intra-cerebral calcification (Figures 1 and 2).

After obtaining this brain imaging, we re-checked serum calcium together with serum phosphorus and

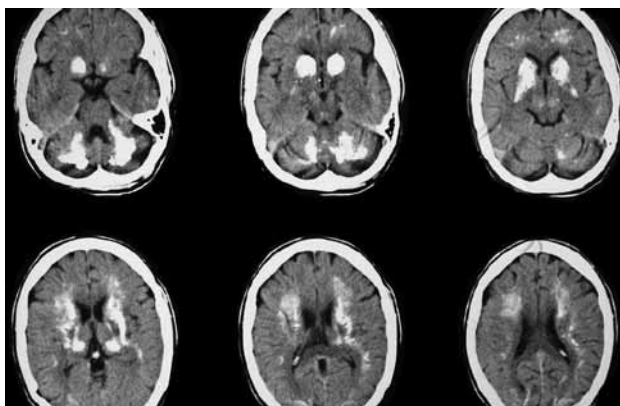


Figure 1: Non-contrast brain CT scan of the patient. It shows bilateral and relatively symmetrical calcification of the basal ganglia, thalami, deep cerebellar nuclei, and white matter of the cerebral hemispheres.

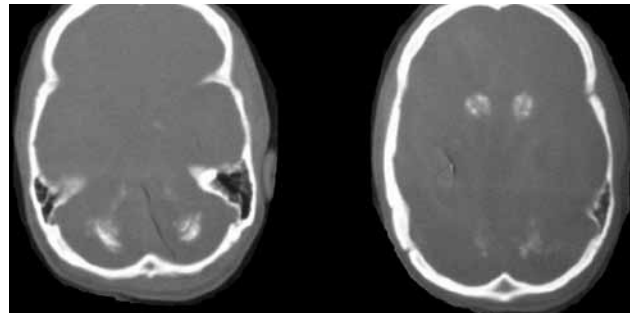


Figure 2: The bone window of the patient's CT brain scan. Note that the calcification flecks at the basal ganglia and the deep cerebellar nuclei can still be seen on this film.

parathyroid hormone; all of these were within their normal reference ranges. The patient was diagnosed with Fahr's disease.

DISCUSSION

Cases of Fahr's disease can be sporadic or familial but have no abnormalities in serum calcium. Furthermore, in those patients, calcium and other mineral deposits could not be linked to a single chromosomal locus. However, in 1993, Martinelli and colleagues reported on several cases of widespread brain calcification within a family and they suggested an autosomal dominant abnormality in vitamin D metabolism (3). Several years earlier, Sly and coworkers reported on 21 cases within 12 families; all of those patients had extensive and bilateral cerebral calcification as well as renal tubular acidosis and osteopetrosis (4). Sly linked the disease to deficiency of carbonic anhydrase II in red blood cells and he suggested an autosomal recessive inheritance. According to Verulashvili, 0.3 to 1.5% of the general population have physiological intra-cerebral calcification, which is entirely asymptomatic and is detected because of the widespread use of CT brain scanning (5). On the other hand, Adams and Victor noticed that ferruginization and calcification of the capillaries of the basal ganglia occur normally in otherwise healthy elderly people to a slight degree than the younger age group, while the occurrence of this calcification in young people should always be taken seriously (6).

In Fahr's disease, calcium deposition occurs bilaterally and symmetrically in the basal ganglia, thalami, deep cerebellar nuclei (mainly the dentate ones), and white matter of the cerebral hemispheres (predominantly at the

centrum semiovale). Therefore, the designation of the disease as striatopallidodentate calcinosis may be more appropriate than Fahr's disease (7).

Most cases of Fahr's disease present with abnormal movements and Parkinsonism; seizures, sub-cortical dementia, and cerebellar dysfunction may be additional features (5). However, Yamada and Hayashi reported on seven members of a family, spanning three generations, aged from five to 57 years, who had bilateral symmetrical basal ganglia calcification and who were otherwise completely normal (8). Kotan and Aygul published a paper in 2009 about a 42-year-old Turkish female with widespread intra-cerebral calcification (9). The patient was healthy and had normal lab tests. The reporters screened her family and found that two of her daughters and three of her brothers had the same CT brain scan finding and normal blood tests.

According to Hecser, the majority of Fahr's patients present between the fourth and sixth decades of life; however, the onset of symptoms in younger patients (as in our patient) and children is not rare (10). Although the parents admitted to noticing the abnormal behavior and mentality of their daughter at the age of 19 years, careful questioning and history taking from her siblings uncovered poor social interaction, non-participation in family events, avoiding everyday house and farm activities, and insomnia starting around the age of 11 years.

In addition to displaying an early onset of Fahr's disease, the cognitive decline (without abnormal movements and seizures) and apathy dominated the clinical picture in our patient. Although the patient had generalized rigidity, no tremor (of any type) was found.

The cognitive decline is consistent with a subcortical type of dementia. This type of dementia is characterized by marked psychosocial incompetence (and minimal memory loss) in the absence of aphasia, agnosia, and apraxia (11). Most patients display a variable combination of forgetfulness, slowing of thought processes, mild intellectual impairment, irritability, depression, apathy, and inability to manipulate knowledge; a picture which resembles frontal lobe dysfunction (12). The memory impairment is highlighted by a prominent deficit of spontaneous recall, rather than problems of encoding and storage of new materials, which is characteristic of the cortical dementias (13).

The diagnosis of Fahr's disease depends on the combination of clinical features, brain imaging findings, and exclusion of other causes of intra-cerebral calcification (such as parathyroid disorders, vascular lesions, toxoplasmosis, syphilis, and systemic lupus erythematosus) (14).

Our patient had diffuse and extensive intra-cerebral calcifications. However, she did not develop the full-blown picture of Fahr's disease. The discrepancy between the imaging findings and clinical features is well-reported. For example, as stated above, patients may be entirely asymptomatic regardless of the degree of calcification (8,9). On the other hand, some patients may develop the fully-fledged Fahr's disease while displaying "minimal" intra-cerebral calcification (15).

We screened the rest of her family (parents and siblings) using non-contrast CT brain scanning; none of them had any form of intracranial calcification. Their ages ranged from 21 years (the youngest sibling) to 56 years (her father). It should be noted that the minimum age at which "negative" CT brain scanning can exclude the disease has not been established yet (16). Genetic testing is not available in Iraq, although the precise role of this investigation is still vague (17).

The parents were educated about the course of the disease and its prognosis and that there is no cure. During the follow-up period of 1 and a half year, the patient had not developed seizures and her cognitive deficits were more or less the same. During the same period, we prescribed alprazolam 0.5 mg to improve her insomnia while her behavioral and cognitive functions were more or less the same on rivastigmine 3 mg/day and sertraline 100 mg/day.

LIMITATIONS

1. The period of follow-up covered a year and a half. The outcome might well have been different if this period of observation was longer.
2. Oral alprazolam was used for short courses, 2-weeks maximum in our patient, to help with insomnia, although the pertinent literature does not support this approach.
3. Rivastigmine, 3 mg per day, was used for the cognitive dysfunction, which seemed to be plateaued on this medication. Other central acetylcholinesterase inhibitors were not tried.

CONCLUSION

Fahr's disease, which is a misnomer, refers to idiopathic bilateral symmetrical basal ganglia calcification and may present as an isolated frontal lobe-like cognitive dysfunction. The brain radiological findings do not predict the clinical presentation and course.

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