Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(11):598-603

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Fahr's syndrome with seizure presentation

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ABSTRACT

Fahr's disease (FD) or Fahr's syndrome is characterized by basal ganglia calcification with clinical manifestations in the form of neuropsychiatric disorders, neurological symptoms, and cognitive symptoms. FD commonly affects young to middle aged adults. The etiology of this syndrome does not identify a specific agent. Clinical manifestations of this disease incorporate a wide variety of symptoms. The diagnostic criteria of Fahr's Syndrome consist of bilateral calcification of basal ganglia, progressive neurologic dysfunction, absence of biochemical abnormalities, infectious, traumatic, and a significant family history. Medical imaging techniques for the diagnosis consist of computed tomography (CT), magnetic resonance imaging (MRI), and plain radiography of the skull. This paper presents a case of Fahr's syndrome in a 60-year-old married prisoner with antisocial personality and seizures. Furthermore, CT and MRI scans showed bilateral symmetric calcifications in the basal ganglia calcification (BGC) and dentate nuclei, cerebellum, and centrum semiovale.

Keywords: Fahr's Syndrome, Basal Ganglia Calcification, Computed Tomography Scan, Magnetic Resonance Imaging.

INTRODUCTION

Fahr's disease (FD) (Fahr's disease or Idiopathic Basal Ganglia Calcifications) is an uncommon neurodegenerative disorder that is characterized by abnormal deposition of calcium in areas of the brain that controls the movements, including basal ganglia, thalamus, dentate nucleus, cerebral cortex, cerebellum, subcortical white matter, and hippocampus (1-3). The clinical manifestations of FD incorporate a wide variety of symptoms Trautner et al., in 1988 suggested that bilateral calcifications are needed with neuropsychiatric and extrapyramidal disorders together with normal calcium and phosphorus metabolism (4). In parallel, another study by Beall et al., in 1989 reported that seizures, rigidity, and dementia disorders correlated with calcification of the basal ganglia (1). In correlation with FD, Flint and Goldstein, 1992 revealed that radiologists may view basal ganglia calcification (BGC) as a chanceful finding (5). In addition, Rasmussen et al. exhibited that incidental discovery of BGC in individuals less than 50 years old may be used to the diagnostic investigation (6). On the other hand, in 1991, Nishiyama et al. reported that the course of mentioned disease is progressive(7). Diagnostic criteria of this disease consist of bilateral calcification

of basal ganglia, progressive neurologic dysfunction, absence of biochemical abnormalities, an infectious, traumatic and a significant family history(8). A study conducted by Manyam et al. suggested that in adult-onset FD and calcium deposition generally begins in the third decade of life together with neurological deterioration two decades later, however, BGC can also occur in pediatric populations (9). Investigations demonstrated that the most usual site of involvement are the basal ganglia and dentate nucleus together with extra pyramidal signs associated with hyperparathyroidism (2). Initiating calcification induced defective iron transport and free radical production, which may cause damage tissue (1, 2). Reduction of blood flow to calcified area associates with clinical symptoms (10). Clinical signs can be developed in the progressive deterioration of mental function, loss of previous motor development, spastic paralysis, optic atrophy, and athetosis(4). Histologically concentric calcium deposits within the walls of small and medium-sized arteries are present. Less frequently the veins may also be affected. Droplet calcifications can be observed along capillaries. These deposits may eventually lead to the closure of the lumina of vessels. The pallidal deposits stain positively for iron (11). Diffuse gliosis may surround the large deposits, but significant loss of nerve cells is rare. On electron microscopy the mineral deposits appear as amorphous or crystalline material surrounded by a basal membrane (12). Calcium granules are seen within the cytoplasm of neuronal and glial cells. The calcifications seen in this condition are indistinguishable from those secondary to hyperparathyroidism or other causes (11). Medical imaging techniques for the diagnosis consist of CT, MRI, and the plain radiograph of the skull (13). Clinical other finding includes blood and urine testing for hematologic and biochemical indices (8). It has been suggested that early diagnosis and treatment can reverse the calcification process leading to complete recovery of mental functions(8).

Case presentation

The patient was a 60-year-old married man living in Kermanshah who were referred to Kermanshah Imam Reza (AS) Hospital from Kermanshah Central Prison due to dyspnea and nonproductive cough and being hospitalized with a primary diagnosis of COPD and CHF in December 2011. The first manifestations of his disease appeared from 3 days ago with dyspnea and chest pain, which were worsening during physical activities. During the rest, the patient had dyspnea, but its intensity was reduced. The patient has not reported but has mentioned the history of lung disease since 1996. The patient has also mentioned no specific drug history, but had the history of using smoke and drugs and his family had no history of a specific disease. The patient has been imprisoned three times since 2007. During a physical examination, his blood pressure, heart pulse, respiration rate, and body temperature were 130/80 mm Hg, 100 per min, 20 breaths per min and 37 C, respectively. The patient was alert during early examinations and pale conjunctiva, rales in chest and + 2 pitting edema in limbs were the only positive finding in the early examinations of patient. The clinical and blood sample assessments showed anemia and normal sodium, potassium and troponin, and International Normalized Ratio (INR) = 1.6 and C-reactive protein (CRP) = +3, as well as evident ischemic variations in electrocardiograph (ECG). The patient was transferred to ICU because of dyspnea with the possibility of pulmonary edema. Furthermore, the performed assessments, showed normal AST, ALT, D-Dimer, ANA, Ds DNA, HBS Ag, Anti HCV, HBC Ab, HIV, C-ANCA, P-ANCA, whereas the calcium and PTH levels were lower than normal, and the patient had Ca = 3.3 mg/dl (normal range= 8.3-11mg/dl), P=9.1 mg/dl (normal range= of 2.5-5 mg/dl) and PTH=3.2pg/dl (normal range= 8.8-76.6 pg/ml) and normal thyroid tests. The echocardiography assessment showed, EF=50%, MR=++, TR=++, mild RV dysfunction, mild PH and PAP=40-45 mmHg. Abdominal and pelvic ultrasonography showed a normal size for kidneys, slightly increased in cortico-medullary echo (Isoechoic to liver) and normal cortical thickness and pyelocaliceal system was organized, which can be a normal finding regarding the patient age. Stone and hydronephrosis were not observed in the scans and other internal organs had normal observed. Generalized tonic-clonic seizure appeared in the patient 15 days after hospitalization, thus he was admitted for brain computed tomography (CT) scan. In the performed non-contrastive CT scan, midline shift and space-occupying lesion were not observed and the ventricular system had normal view. Furthermore, bilateral symmetric calcifications in the basal ganglia and dentate nuclei, cerebellum and white matter of bilateral centrum semiovale as well as bilateral occipital lobe gyruses were observed. Regarding the above clinical and neuroimaging manifestations, the Fahr's syndrome was diagnosed for the patient. The consciousness level of the patient gradually decreased and because of severe respiratory distress and pulmonary edema, he was intubated, but finally the patient died.

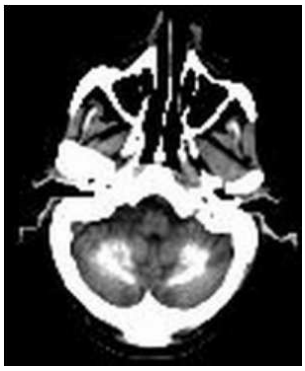

Figure 1. 60 year old male with Fahr's syndrome. CT axial images, at the level of the cerebellum showing hyperdens area (calcification). Spiral CT scan, axial, 5 mm slice, KVP 1.4, exposure 300

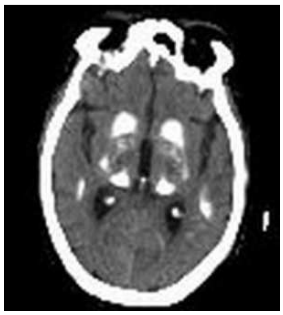

Figure 2. 60 year old male with Fahr's syndrome. CT axial images, at the level of the third ventricular showing hyperdens area (calcification) in caudate and lenticular nucleus and thalamus. Spiral CT scan, axial, 5 mm slice, KVP 1.4, exposure 300

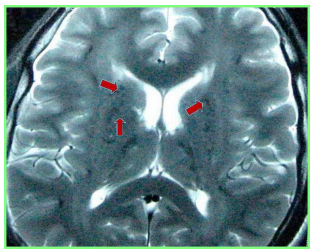

Figure 3. 60 year old male with Fahr's syndrome. MRI axial T2 images at the of low ventricular level showing hypointense area (calcification) in the region of the basal ganglia (arrow). MRI: 1 Tesla magnet, T2 axial image (TE= 94, TR= 9000), 5 mm slice

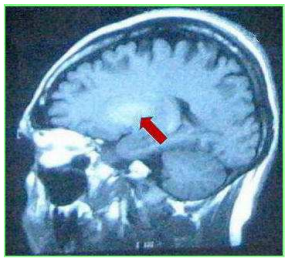

Figure 4. 60 year old male with Fahr's syndrome. MRI coronal T2 images, at the level of body of lateral ventricle showing hypointense area (calcification) in the region of the basal ganglia (arrow). MRI: 1 Tesla magnet, T2 sagittal image (TE= 99, TR= 3000), 5 mm slice

DISCUSSION

FD which was first introduced by Karl Theodor Fahr in 1930 (14) is a rare neurological degenerative disease characterized by the presence of bilateral symmetric calcifications over the basal ganglia, dentate nuclei, cerebellum

as well as bilateral centrum semiovale. In this disease, abnormal deposit of calcium (calcification) in areas of brain controlling movement (basal Ganglia and cerebral cortex) causes the loss of related cells, and this disease is associated with normal serum levels of calcium and phosphorus in patient (15). Basal ganglia and dentate nucleus are the most common sites of involvement and most of patients manifest extrapyramidal symptoms. The disease is often associated with abnormal phosphocalcemic metabolism especially with hypoparathyroidism(16).

Etiology & Demographics

The exact etiological manifestations remain unknown yet but an association with specific etiologies include endocrine disorders (e.g. hypoparathyroidism and Hyperparathyroidism), adult onset neurodegenerative conditions (e.g. neurodegeneration, iron accumulation disease, polycystic lipomembranous and leukoencephalopathy), infectious disease (e.g. cockayne syndrome Types 1 and 2), and Inherited or early onset syndrome (e.g. Aicardi-Goutieres syndrome, Tuberous sclerosis complex, Brucellosis, and Coat's disease) (8). Defective iron transport and free radicals production initiate calcification process. FD in adults initiates with generalized deposit of calcium in the third decade and neurological complications become manifest after two decades. Disease symptoms develop when deposits are accumulated and include progressive complications of brain function, loss of prior motor movements, spastic paralysis and athetosis. Optic atrophy may also occur (16).

Clinical & Imaging Findings

These patients refer in their youth with psychosis symptoms (hallucinations, delusions) similar to schizophrenia (17) and symptoms of dementia and movement disorders as Parkinsonism, athetosis chorea and negative symptoms of schizophrenia are seen in their older ages (17, 18). Low IQ is another symptom of this syndrome. Coincidence of this syndrome with Down syndrome has also been reported in the performed study (17). FD is diagnosed based on the presence of symmetric calcifications involving basal ganglia (bilateral striopallidodentate calcinosis - BSPDC) with normal serum levels of calcium and phosphorus (19).This disease is distinguished from Fahr's syndrome in which basal ganglia calcifications have specific causes (such as hypoparathyroidism) and also from normal calcifications in the basal ganglia without clinical symptoms and known reason, which is an incidental finding observed in 0.7 to 0.9 percent of populations and mainly in ages over 60 (20). The most common sites of calcification are putamen, caudate nucleus, internal capsule, dentate nucleus, cerebellum, thalamus, and cerebellar white matter. Calcium deposit occurs in extracellular and extravascular space surrounding the capillaries (15). FD can be associated with a wide variety of clinical symptoms including psychotic disorders, seizure and dementia but other symptoms such as syncope and pseudo hypoparathyroidism have also been observed. Benke et al. studied brain metabolism of a patient with Fahr's syndrome with dementia of the frontal lobe and dominant frontal lobe syndrome manifestations using F-18 FDG Positron Emission Tomography (PET). Dramatic reduction of glucose metabolism in basal ganglia and frontal lobe including orbito-frontal and anterior cingulate regions were consistent with psychotic and personality disorder symptoms of the disease (8, 21) (Table 1). An autosomal dominant inheritance was observed in familial cases in genetic studies (22). A polygene inheritance is identified by linking to the IBGC1 locus on chromosome 14q, but the causative gene is not known yet. CT scan is the most effective way of screening in adults (23). No distinct psychiatric and neurological symptoms were observed in the first-degree relatives of patient. Although the subjects undergo CT scan, radiologic signs of disease may be present in them. Additionally, most frequently affected area is the lenticular nucleus, especially the internal globuspallidus while Cerebellar gyri, brain stem, centrum semiovale, and subcortical white matter may also affected. Calcifications in the putamen, thalami, caudate, and dentate nuclei are also common. Occasionally, calcium deposits begin or predominate in regions outside the basal ganglia. Calcification seems to be progressive and gradual.

Treatment & prognosis

FD is a rare disease with no absolute treatment and the aim is an adjunctive therapy. Therefore, more rapid diagnosis of it with imaging techniques is recommended. L-dopa (or carbidopa) and antipsychotic drugs are prescribed for Parkinson and psychotic symptoms, respectively. Furthermore, Seizures and movement disorders in Fahr's syndrome which are related to the parathyroid disorder can be resolved with the correction of phosphate and calcium levels for e.g. treatment with alpha hydroxy vitamin D3 and corticosteroids reversed neurological deficits (24). To summarize, though Fahr's syndrome and FD are rare entities they should be suspected in patients with neuropsychiatric disturbances and seizure disorder. Routine biochemical investigations should always be performed to rule out metabolic causes. Conversely, all patients with incidentally detected striopallidodentate calcinosis should be subjected to thorough neuropsychiatric examination and if required, biochemical tests. Knowledge of the associated conditions will not only help to rectify the treatable cause but will also prevent unnecessary treatment in others. There have been many major advances in our understanding of Fahr's syndrome, especially in terms of

etiology, the breadth of the disease phenotype and diagnostic methods. There is no simple solution to this dilemma and controversy. Certainly more qualitative and quantitative data on the experience of families are needed. Their voice - while reflecting one aspect of the whole portrait - is crucial and vital. Secondly, international consensus on guidelines for care that includes all of the specialties involved in the care of children and elder people with Fahr's syndrome is required. Thirdly, Continuation of the now ongoing dialogue on this topic by neurologist, geneticists, psychiatrist, families, and the appropriate care specialists is mandatory and welcomed. Has been suggested the pathophysiological mechanisms leading to bilateral calcification. Only rare data are available on the early events leading to bilateral calcification. Furthermore, physicians play a crucial role the effective treatment of the disease. Currently, available medications are either poorly effective and/or have bad tolerance.

Table 1. Clinical features of Fahr's syndrome could vary with the age and course of disease (8).

System		Clinical properties
1	Neurological	Loss of consciousness Tetany Seizures Epileptic disorder Gait disorder Spasticity Speech impairment Dementia Myoclonus Coma Paroxysmal choreoathetosis Dystonic choreoathetosis Papilledema of intracranial hypertension Pleocytosis of CSF
2	Movement disorder	Clumsiness Fatigability Unsteady gait Involuntary movements and muscle cramping
3	Neuropsychiatric features	Psychosis Depression Apoplexia Deterioration of intelligence Inability to make decisions

CONCLUSION

Although the clinical symptoms of this disease are mostly as motion and cognitive disorders, depression and psychosis resulting from it are rather common. Parkinsonism, chorea, dystonia, tremor, gait disorders, dysarthria, seizures, and myoclonus are the most common neurological picture and fronto-subcortical type is the cognitive impairment picture. It is observed that the patient has been jailed repeatedly due to antisocial behaviors. This behavior and personality of the patient, especially in older ages may be caused by this syndrome. The diagnosis of Fahr's syndrome requires the presence of certain clinical criteria that may confuse the diagnosis with other aspects. New treatment methods need to be discovered and employed to reduce functionality associated with the disease. It's especially important to consider genetic counseling of known at risk parents before conception. Screening asymptomatic individuals has not been able to demonstrate immediate medical benefits in adults or young individual's. The screening of young individuals is considered unnecessary, can have profound psychological harm effects.

Acknowledgements
The authors would like to acknowledge the Kermanshah Imam Reza hospital officials for their support and contribution in to this study.

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