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Fahr's Disease with a Thirty Years History of Seizures

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1. Abstract

Fahr's disease/Fahr's syndrome is a rare neurological disorder characterized by symmetrical calcification in various brain parts, most commonly in the basal ganglia. We report a case of Fahr's disease in a 72-years-old female who presented with delirium. Upon further evaluation, she had a history of seizures for thirty years, dementia for eighteen months, extrapyramidal symptoms for one year and psychiatric symptoms for six months. We diagnosed this case as Fahr's disease and managed in the intensive care unit and wards. We discharged her with medications like tetrabenazine, quetiapine, clonazepam, atorvastatin, donepezil, sodium valproate, vitamins and mineral supplements. We followed her progress for seven months. Her motor and neuro-psychiatric recovery during the period has been encouraging. This report highlights the importance of screening for Fahr's disease in any case of seizure and bilateral brain calcification, which is highly overlooked and misdiagnosed in our part of the world.

2. Keywords: Basal ganglia; Calcification; Fahr's disease

3. Introduction

Fahr's syndrome/Fahr's disease/Idiopathic basal ganglia calcification is a rare neurological disorder characterized by bilateral and symmetrical calcifications in different brain areas like basal ganglia, thalamus, dentate nucleus and cerebral cortex. Clinical manifestations range from dementia, neuropsychiatric symptoms, extrapyramidal symptoms, to cerebellar signs. Our case is unique due to a 30 years history of undiagnosed seizures and a broad range of clinical manifestations in a single person. We report a case of a 72-years-old female who presented with a history of seizures, dementia and motor problems like tremors and rigidity.

4. Case Presentation

A 72-years-old female presented to the emergency department of Venus hospital in a delirious state and inability to feed for the last three days. Her level of consciousness, according to the Glasgow Coma Scale, was 10/15 (E3M5V2). Her blood pressure was 80/50 mm of Hg, respiratory rate was 15 per minute and the temperature was 98 degrees Fahrenheit. Her breath sounds were normal vesicular and heart sounds were also within normal limits. She had mild pallor, but no icterus, cyanosis, clubbing, lymphadenopathy and edema. She appeared dehydrated with dry mouth and decreased skin turgor. We could not evaluate mental

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scoring as she was disoriented and was producing incomprehensible sounds. She appeared emaciated with reduced muscle bulk in all muscle groups, power in all limbs was 3/5, tone increased, bilateral resting tremors present in hands. There was no history of trauma, fever, recent abnormal body movements, frothing and toxin ingestion.

She was apparently in her usual state of good health 30 years back when she started having frequent episodes of generalized tonic-clonic seizures. She visited a nearby hospital, where they performed a Computed Tomography scan of the head, which showed no abnormalities. The treating physician prescribed her with phenytoin at a 300 mg dose per day, which she took for ten years. The seizures were under control within that period and the medication was gradually tapered and stopped. No seizures occurred for the next ten years. Then she had a fainting episode after 20 years of being seizure-free. The fainting spells were characterized by loss of consciousness for four to five minutes without any abnormal body movements. She underwent a CT scan of her head again, which showed calcifications in the bilateral basal ganglia. She subsequently resumed phenytoin, which controlled her symptoms.

Eighteen months before the presentation in our hospital, she started having memory loss of recent events, which progressed to retrograde amnesia over six months. One year back, she developed bilateral mild resting tremors in her hands, followed by tremors in her head. This was accompanied by neuropsychiatric symptoms like agitation, changes in behavior, irrelevant statements, wandering outside and visual hallucinations (She repetitively talked about a child who was actually not present). Motor symptoms worsened to slurring of speech, dysphagia, weakness and stiffness of all four limbs over six-month duration. She was taken to another hospital where a Magnetic Resonance Imaging scan of the head was ordered. The MRI revealed few calcifications; however, most calcifications went undetected since the MRI did not include susceptibility-weighted imaging. Then she was prescribed with the medication's donepezil and sodium valproate for dementia and seizures, respectively. However, there was no clinical improvement. She was progressively bed-ridden and could not even open her mouth to eat for the last three days.

The patient has a ten-year history of hypertension under medication. Family history were positive in her mother, who had bilateral resting tremors of the hands and head with stiffness in all limbs, but no dementia and psychiatric symptoms.

We admitted the patient in the intensive care unit, started rehydration with intravenous fluids and provided other supportive management.

We sent baseline investigations, ordered plain computed tomography head, chest X-ray and electrocardiogram. A lumbar puncture was done and cerebrospinal fluid was sent for analysis. CSF analysis showed normal cell count, glucose, protein and no growth in culture. Chest X-ray and ECG appeared normal.

Laboratory findings were within normal limits as listed in the Table 1.

Table 1: Laboratory findings of the case.

Investigation	Value	Normal range
Total Leukocyte count	3690 cells/cumm	4500 - 11000 cells/cumm
Hemoglobin	12.0 gm/dl	12 - 16 gm/dl
Platelets count	189000/cumm	150,000 - 350,000 /cumm
Urea	39.0 mg/dl	13 - 43 mg/dl
Creatinine	0.7 mg/dl	0.4 - 1.2 mg/dl
Sodium	142 meq/l	135 -145 meq/l

Potassium	3.7 meq/l	3.6 - 5.5 meq/l
Free tri-iodothyronine (FT3)	3.26 pg/ml	2.0 - 4.2 pg/ml
Free tetraiodothyronine (FT4)	1.84 ng/ml	0.89 - 1.72 ng/ml
Thyroid-stimulating hormone (TSH)	0.21 µIU/ml	0.3 - 4.5 µIU/ml
Calcium	7.9 mg/dl	8.1 - 10.4 mg/dl
Phosphorous, Inorganic	3.4 mg/dl	2.5 - 5.0 mg/dl
Intact Parathyroid Hormone (IPTH)	31.50 pg/ml	40-65 pg/ml
Vitamin D (25 Hydroxy)	23.48 ng/ml	20-40 ng/ml
Vitamin B12	330 ng/ml	200-900 ng/ml

Plain Computed Tomography Scan of the head shown in Figure 1 revealed extensive areas of homogeneously dense calcifications involving the bilateral centrum semiovale, periventricular region, basal ganglia region and dentate nuclei as well as cerebellar hemispheres symmetrically. However, no obvious features of cerebral atrophy and mass effect were seen.

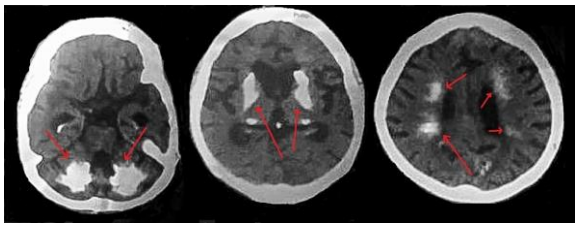

Figure 1: Plain Computed Tomography scan of the head showing bilateral calcification in various regions of brain.

The following diagnostic criteria are well established [1-3]

Diagnostic criteria for Fahr's disease

- Bilateral calcifications of the basal ganglia or other areas of the brain on neuro-imaging.
- Progressive neurological dysfunction and/or psychiatric symptoms.
- Onset between the ages of 40 to 50.
- Absence of biochemical abnormalities and somatic states suggestive of metabolic or mitochondrial disease.
- Absence of toxic, infectious or traumatic causes of intracranial calcifications.
- Positive family history of Fahr's syndrome and/or proved genetic background.

The blood pressure and dehydration were corrected and we shifted the patient from the ICU into the general ward. We prescribed medications like tetrabenazine, quetiapine, clonazepam, atorvastatin, donepezil, sodium valproate, vitamins and mineral supplements. She was discharged after 15 days of hospital stay. We followed up with the patient regularly for seven months. She started having improvement in the tone and strength of the muscles within two months. Tremors gradually improved. She gradually regained her memory, firstly short term and immediate memory. Now she has no issue with her memory except for interval amnesia of six months during her peak illness. Psychiatric symptoms also subsided over two months. She occasionally complained about the "imaginary child "during the last two months, but is otherwise doing well.

5. Discussion

Fahr's disease is a rare neurological disease characterized by abnormal, bilateral and symmetrical calcium deposition in different areas of brain. It can be of familial origin or sporadic, with a prevalence of less than one in one million [4]. Most familial cases are autosomal dominant and few are autosomal recessive. The exact cause is yet unknown, but some studies have described the mutations in the genes which cause problems in phosphate ion channels and free radical damage resulting in calcification [5]. calcification starts from the perivascular space and extends to cover the adjacent brain tissue [5]. German scientist Karl Theodor Fahr's reported case for the first time, so the name was given after him [6].

Calcification in the brain can be due to a primary cause or a secondary cause. The calcified deposits mainly consist of calcium carbonate, calcium phosphate, mucopolysaccharide and metals like iron, copper, magnesium [7]. Some literature refers to primary calcification as Fahr's disease and secondary calcification as Fahr's syndrome [8]. Primary calcification is genetically predisposed, autosomal dominant being the most common mode of inheritance. Studies have found mutations in several loci, one of the most common mutations being the loss of function mutation in the gene encoding sodium-dependent phosphate transporter (SLC20A2) on chromosome 8p. Some studies have identified the mutation of a locus on chromosome 14 [9].

Secondary causes include idiopathic hypoparathyroidism, secondary hypoparathyroidism, pseudohypoparathyroidism, hyperparathyroidism, vitamin D disorder, Kenny cafe syndrome and many others [1].

Usually, symptoms begin to appear at 40 to 50 years in primary disease [4,5]. Only a few among many people with brain calcifications similar to Fahr's disease develop symptoms. Guilia et al. refer this to heterogeneity in gene mutation among different people [10]. Even people in the same pedigree with the exact mutation have variable presentations. This might be due to the variable penetrance and expressivity of the mutated gene and the resilience of the individual brain [10]. symptoms can be broadly categorized into movement disorders, neurological problems and psychiatric problems. Movement disorders include a spectrum of symptoms ranging from clumsiness, dystonia, chorea, gait disorder, slurred speech, dysphasia and tremor to frank parkinsonism. Neurological symptoms include seizures, dementia, loss of consciousness and sometimes coma. Psychiatric symptoms also range from minor changes in personality and behavior, cognitive decline, depression, mania-like symptoms to schizophrenia [1]. Our patient had neurological, psychiatric and motor symptoms, which is rarely reported.

Fahr's disease is a diagnosis of exclusion. Any bilateral brain calcification should be followed by the evaluation of endocrine, neoplastic, infectious and congenital (tuberous sclerosis) causes. Diagnostic criteria are described and modified over the years, which is mentioned above in the case presentation. Management of Fahr's syndrome requires the collaborative effort of neurologists, psychiatrists, endocrinologists and physiotherapists. The definitive cure is yet not available, but the patient can be benefited with symptomatic management, which includes antiepileptics for seizures, antipsychotics for psychosis, SSRI for behavioral symptoms and depression and neuroleptic for movement disorders. Physical rehabilitation plays a significant role in strengthening muscles, preventing contracture and improving postural stability.

In this case report, we present the clinical manifestation of Fahr's disease over a period of 30 years, hospital course and follow-up over 7 months. Our patient had symptoms ranging from neurological, psychiatric to motor dysfunction. This report suggests us to understand the clinical progression that can occur over the years with all ranges of manifestations in a single person. Although our study's follow-up time is short, the clinical recovery of our patient over seven months is the subject of further study in the prognosis of Fahr's disease. Our study lacks the investigation to rule out the mitochondrial cause of encephalopathy and the patient and her family members' genetic evaluation. Being a rare disease, Fahr’s disease is highly overlooked and misdiagnosed in our part of world. As such, this case went misdiagnosed for 30 years from the time of symptom onset.

We conclude with a message that any patient with a history of seizures with bilateral and symmetrical calcifications of the brain should be evaluated for Fahr's disease/syndrome.

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