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Case report

RARE ASSOCIATION OF FAHR'S DISEASE WITH MULTIPLE MYELOMA: A CASE REPORT

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ABSTRACT

Fahr's disease or Fahr's syndrome is a rare neurological disorder characterized by abnormal calcified deposits in the basal ganglia and cerebral cortex. 47 years male who presented to us with progressive ataxia and Parkinsonian symptoms was found to have extensive bilateral calcifications including bilateral basal ganglia in CT scan of the brain. The secondary causes of intracranial calcifications were ruled out to make a clinical diagnosis of Fahr's disease. While investigating for chronic low back pain with anemia and renal failure, high ESR and serum protein electrophoresis showing M band was detected. On further investigation, the bone marrow study confirmed the diagnosis of multiple myeloma. There are only few case reports of association of Fahr's disease and multiple myeloma in literature. The case is being reported here in view of rarity.

Key words: Fahr's disease, Bilateral intracranial calcifications, Multiple myeloma, M-Band, Plasma cells.

INTRODUCTION

Fahr's disease was first described by a German neurologist Karl Theodor Fahr in 1930^{1,2} and is characterized by abnormal deposition of calcium in areas of brain that control movements including basal ganglia, thalamus, dentate nucleus, cerebral cortex, cerebellum, sub-cortical white matter and hippocampus. The clinical pattern is variable and the disease may be sporadic or Familial. Genetically a locus at 14q has been suggested.³ A second locus has been identified on chromosome 8⁴ and third one on chromosome 2, suggesting genetic heterogeneity in this disease.⁵ The disease usually appears between the age of 40-60 years.¹ Neuropsychiatric, extrapyramidal and cerebellar symptoms, convulsive seizures, parkinsonian features; dementia and speech disorders may accompany clinical manifestations. Diagnostic criteria of Fahr's syndrome has been modified and derived from Moskowitz et al⁶ (1971), Elie et al⁷ (1989) and Manyam⁸ (2005) and can be stated as follows: 1. Bilateral calcification of basal ganglia

visualized on neuroimaging. Other brain regions may also be involved. 2. Progressive neurologic dysfunction, which generally includes a movement disorder and or neuropsychiatric manifestation. Age of onset is usually in the fourth or fifth decade, although this dysfunction may also present in childhood. 3. Absence of biochemical abnormalities and somatic features suggestive of mitochondrial or metabolic disease or other systemic disorder

CASE REPORT

A 47 years Hindu male from middle socioeconomic status, married and working as a clerk presented to us in the Dept. of Medicine, with progressive unsteadiness in walking and clumsiness of hands for around three years. It was associated with memory loss and emotional outbursts. Initially the symptoms were slowly progressive and he was able to do his daily activities. But he became more symptomatic

around 3 months prior to presenting to us. There was progressive stiffness of limbs with a tremor of hands and head nodding. Memory loss was progressing and limb movements became slower and restricted so that he was almost confined to a chair. Speech became more and more dysarthric and social interaction became more difficult. There was moderate to severe back pain for around three months at the time of hospitalization. Around two weeks prior to hospital admission he was almost bed ridden because of stiff limbs and back pain. There was no history of head injury or seizure disorder. He was non-diabetic and non-hypertensive, non-alcoholic but occasional smoker. His father had some movement disorder which started at around age of 50 years and he died at the age of 60 years. No other sibling had any movement disorder or similar symptoms. He was treated with vitamins and neuro-protectives from time to time without any improvement.

On examination he was conscious, oriented, of average body built with pulse rate of 70/min and regular and Blood Pressure 130/80 mm of Hg. There was pallor but no icterus, cyanosis, clubbing or lymphadenopathy. Pedal edema was absent and Jugular venous pressure was not raised. On examination of Central nervous system, he was conscious and oriented with impaired recent memory but intact past memory with mini mental score of 22. Speech was dysarthric with presence of released reflexes. There was no cranial nerve involvement or nystagmus and motor examination revealed normal bulk and power with tremor of hands, rigidity in both upper and lower limbs and all deep tendon jerks in both upper and lower limbs were brisk and plantar was bilaterally extensor. There were cerebellar signs in both upper and lower limbs. There was no sensory abnormality and skull and spine examination revealed no abnormality except tenderness over lumbar vertebrae. Cardiovascular system, chest and abdomen examination revealed no abnormality. With a provisional diagnosis of parkinsonism-dementia complex and cerebellar dysfunction he was planned for thorough investigation.

On routine pathological tests Hb was 3.7G%, total leucocyte count was 9,600/cmm with neutrophil 86%, lymphocytes 12%, and eosinophil 2%. ESR was 120 mm 1st hour. Comment on peripheral smear showed microcytic hypochromic anemia and routine microscopic examination of urine was within normal

limits. Routine biochemical tests showed blood urea 62 mg/dl, serum creatinine 6.5 mg/dl, serum sodium-137 meq/L, potassium 4.5 meq/L and calcium 8.9 meq/L. Fasting and postprandial plasma sugar was 112mg/dl and 148 mg/dl respectively. Serum parathormone (PTH) was 32 ng/L (range 8-50) and Thyroid function test was within normal limits. Serum protein electrophoresis showed M-Band. (Fig 1) Further bone marrow study showed plasma cell infiltration confirming diagnosis of multiple myeloma. (Fig 2)

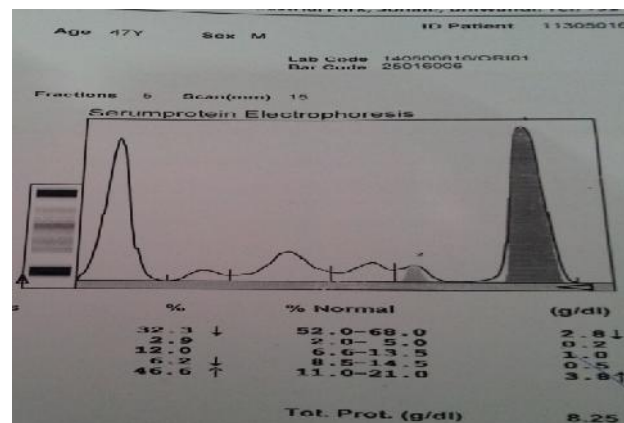


Fig 1: Serum protein electrophoresis showing M Band

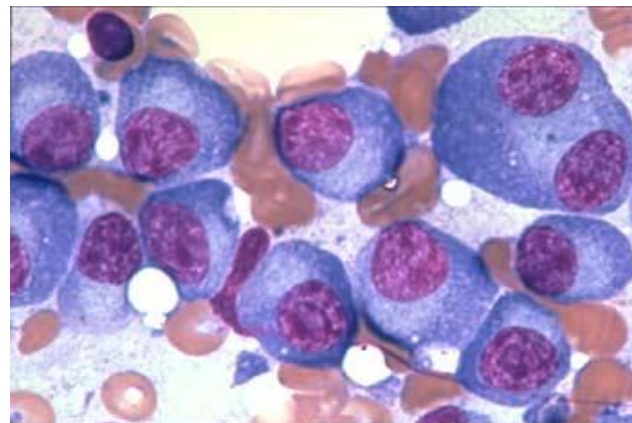


Fig 2: Bone marrow showing plasma cells

Radiological imaging revealed hepatosplenomegally with reduced cortical-medullary differentiation in the kidney on ultrasonography of the abdomen and X-Ray of chest, skull and pelvis was normal. Non-contrast Computerised Tomography (NCCT) (Fig 3,4) scan of brain showed multiple and diffuse calcification in bilateral basal ganglia, cerebellar hemispheres, pons, thalamus, internal capsule and cerebral hemispheres and diagnosis of Fahr's disease was considered. Finally the case was diagnosed as a case of Fahr's disease with multiple myeloma with nephropathy and anemia. Neurological symptoms were treated conservatively. Oncologists help was sought for multiple myeloma and chemotherapy was

started. Four weeks after starting chemotherapy he developed severe sepsis with multi-organ dysfunction with septic shock and succumbed. Prognosis of Fahr's disease is variable and there is no reliable correlation between age, extent of brain calcification and neurological deficit. Progressive neurological deterioration is invariable and results in disability and death.

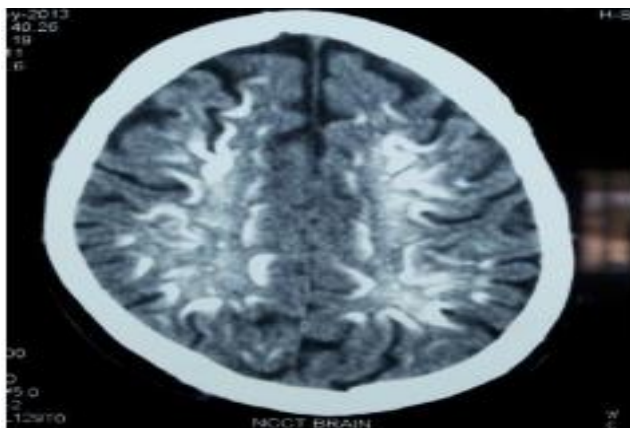


Fig 3: CT Scan of Brain showing calcification in bilateral basal ganglia and sub cortical white matter



Fig 4: CT scan of brain showing bilateral cortical calcification

DISCUSSION

Fahr's disease otherwise known as bilateral striopallido dentate calcinosis (BSPDC) or idiopathic basal ganglia calcification is a rare neurodegenerative disorder of unknown prevalence. This is among the few inherited neurological conditions that lead to progressive dystonia, Parkinsonism and neuropsychiatric manifestations. As Fahr's disease is a progressive neurodegenerative disorder of unknown

etiology, till now there is no definite cure and treatment is symptomatic.⁶

The most common presentations as per the Fahr's disease registry are movement disorders, which account for about 55% of cases. Among these, parkinsonism was seen in 57% cases, chorea was seen in 19% cases, tremor in 8% cases, dystonia in 8% cases, athetosis in 5% cases and orofacial dyskinesia was seen in 3% case. The other neurologic manifestations include cognitive impairment, cerebellar signs, speech disorders, pyramidal signs, psychiatric features, gait disorders and sensory changes. Various clinical conditions coming as differential diagnosis to Fahr's disease are Parkinson's disease, Juvenile parkinsonism, other causes of secondary Parkinsonism like post encephalitic parkinsonism, slow virus infection, drug induced parkinsonism, multi-infarct dementia with parkinsonism, Multisystem degeneration, Huntington's disease and Lewy Body disease⁷

Calcification generally develops within the vessel wall and in the perivascular space, ultimately extending to the neurons. Progressive basal ganglia mineralization tends to compress the vessel lumen, thus initiating a cycle of impaired blood flow, neural tissue injury and mineral deposition.¹ Deposits are composed of minerals like calcium phosphate and carbonate, glyconate, mucopolysaccharide and metals including Iron, Copper, Magnesium, Zinc, Aluminum, silver and cobalt may also be found.^{8,9} Treatment of Fahr's disease is only symptomatic. Various drugs are used to improve anxiety, depression, obsessive compulsive disorder and to alleviate dystonia. Oxybutinin used for urinary incontinence and antiepileptics for seizure. Haloperidol and lithium carbonate may help in psychotic symptoms. Levodopa therapy for parkinsonism shows poor response.¹⁰⁻¹²

The etiology of this syndrome does not identify a specific agent, but associated with a number of conditions has been noted. Most common of which are endocrine disorders, mitochondrial myopathies, dermatological abnormalities and infectious diseases. Among endocrine disorders parathyroid disturbances are most commonly associated with Fahr's syndrome.¹ The abnormalities include idiopathic hypoparathyroidism, secondary hypoparathyroidism, pseudohypoparathyroidism, pseudo-pseudo hypoparathyroidism and hyperparathyroidism. Other

conditions associated with Fahr's syndrome are Kenny Caffey Syndrome Type-1, Mitochondrial myopathies like Kearns-Sayre Syndrome and MELAS (myopathy, encephalopathy, lactic acidosis and stroke), adult onset neurodegenerative conditions like neuroferritinopathy and polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, dermatological conditions like lipid protenosis, Intrauterine or perinatal infections like toxoplasmosis, rubella, CMV or Herpes virus infection. Cockayne syndrome, Aicardi-Goutieres Syndrome, Tuberous sclerosis complex, Brucellosis and Coats disease is also associated with Fahr's syndrome.¹ There is no definite treatment available to achieve remission or stabilization of Fahr's disease. Management is only symptomatic with drugs and physiotherapy.¹

But case report showing association of multiple myeloma and Fahr's syndrome is few in literature. Nishiyama et al in 1991 have first reported a 41 year old woman with Fahr's disease associated with multiple myeloma.¹³ The initial symptom of dystonia and spasticity in the left leg started when she was 30 years old. M proteinemia was detected when she was 32 years and multiple myeloma when she was 40 years old. Periodical CT scans revealed that the intracerebral calcifications had worsened gradually through 8 years. Kenji Isoe et al also reported the case of a 66 yr old man with dementia, dysarthria, rigidity, pyramidal signs and truncal ataxia with calcification in basal ganglia, floor of cortices, subcortical white matter and cerebellum associated with IgG M proteinemia (MGUS).¹⁴ The patient had also calcification of aorta, pleura, pericardium and diaphragm. Tentolouris et al have reported three cases of familial calcification of aorta and calcific aortic valve disease associated with monoclonal chain gammopathy.¹⁵ They had indicated that immunological abnormalities were associated with calcifications. Our case is one among the rare case reports of association of Fahr's syndrome with multiple myeloma or MGUS and we also believe there may be some immunological basis associated with diffuse calcifications of Fahr's syndrome which needs further studies.

CONCLUSION

Fahr's disease or Idiopathic basal ganglia calcification is a rare neurological disorder with autosomal dominant transmission. Diagnosis is based

on some clinical criteria, calcifications in bilateral basal ganglia and other cortical and sub cortical structures on neuroimaging and exclusion of other pathological conditions causing bilateral intracranial calcifications. Progressive neurological deterioration generally results in disability and death. Treatment is only symptomatic and prognosis is variable. This disorder is associated with a variety of other metabolic, endocrine and genetic disorders, but no specific etiology has been identified yet. From the various case reports of association of multiple myeloma with Fahr's disease or diffuse calcification of aorta and aortic valves including our case report it appears that there is some immunological basis to the development and progression of calcification in Fahr's disease. Further study is required to find out exact molecular mechanism involved which may also lead to exploration of therapeutic options.

Conflict of interest: None

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