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FAHR'S SYNDROME IN A PATIENT WITH PSEUDOHYPOPARATHYROIDISM – AN INTERESTING CASE REPORT

Neurology

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ABSTRACT

Fahr's Syndrome is a rare neurodegenerative disease which is characterized by bilaterally symmetrical calcifications in various parts of the brain such as the basal ganglia, cerebellum, thalamus, cerebral cortex etc. It can have a wide variety of clinical presentations ranging from, dementia, parkinsonism, movement disorders etc. It can be primary/idiopathic or secondary to other causes mainly endocrinopathies. Here we describe an interesting case of a 78 years old man who presented with dementia and tremors and was later diagnosed as fahr's syndrome which was secondary to pseudohypoparathyroidism.

KEYWORDS

Fahr's syndrome, Pseudohypoparathyroidism, Cognitive, Parkinsonism

INTRODUCTION

Fahr's syndrome is a rare neurodegenerative disorder which is characterize by benign, non-atherosclerotic bilaterally symmetrical intracranial calcifications involving the basal ganglia, dentate nucleus of cerebellum, thalamus, cerebral cortex etc. [1]. It was first described in the year 1930 by Karl Theodor Fahr who was a German neuropsychiatrist [1]. Fahr's syndrome can be of two types- Primary or idiopathic variety also called as Fahr's disease (Idiopathic basal ganglia calcification/Strio-pallido-dentate calcinosis) which is the familial variant and is having autosomal dominant inheritance, but it may also be passed on as an autosomal recessive trait or it may occur sporadically [2]. Recently studies have shown that a locus at gene 14q to be involved in the pathogenesis of the disease [3].

And a secondary variety which is also called fahr's syndrome and is seen in association with other disease particularly abnormalities of calcium and phosphate metabolism and endocrinopathies (hypoparathyroidism, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism etc.) though it can also be seen in association with toxins, infections, mitochondrial myopathies etc. [1]. The usual age of onset is in the 3rd to 4th decades of life.

Clinically it can have a wide variety of neurological and neuropsychiatric manifestations ranging from dementia, parkinsonism, movement disorders like chorea, seizures, ataxia, speech disorders, psychosis etc. [1,4].

Diagnosis is based on the demonstration of classical calcification pattern in the brain on CT/MRI scan in the presence of progressive neurological or neuropsychiatric symptoms.

Pseudohypoparathyroidism (PHP) is a rare metabolic disease which is characterized by end organ resistance or unresponsiveness to the action of parathyroid hormone and many other hormones. The syndrome mimics hypoparathyroidism with patients experiencing hypocalcemia and hyperphosphatemia, however unlike hypoparathyroidism, in PHP the PTH levels are high. PHP is subclassified into types Ia, Ib, Ic and type II [5]. PHP (Ia,Ic) are associated with a constellation of phenotypic features including short stature, obesity, round face, short neck, shortened metacarpals, brachydactyly etc. This is called Albright's Hereditary Osteodystrophy (AHO) [5].

We describe a case of an old man who presented with progressive dementia and tremors and was diagnosed as fahr's syndrome based on the clinical and radiographic evaluation which was then found to be caused secondary to pseudohypoparathyroidism.

CASE STUDY

A 78 years old previously healthy man presented to the outpatient department with complains of frequent forgetfulness, in-attention, poor concentration, irritability, feeling of low mood etc. for the last 5- 6 years which has worsened over the last 2 months. There was no history of similar complains in the past. He did not had history of any chronic diseases. There was nothing significant in family history. No history of smoking, alcohol, addiction etc.

On general examination of the patient the patient was conscious, oriented, cooperative. Had average built. None of the features suggestive of Albright's Hereditary Osteodystrophy was present. His vitals were stable.

On neurological examination he had mini-mental status examination (MMSE) score of 16/30 and Mini-Cog score of 2/5 which was suggestive of moderate cognitive impairment. There was presence of resting tremors, bradykinesia, rigidity and mask like facies. Rest of the motor system, sensory system and cranial nerve examination was normal. Routine laboratory examination such as hemogram, RBS, LFT, KFT, lipid profile was within normal limits.

NCCT (Brain) was done which revealed extensive bilaterally symmetrical calcifications involving the basal ganglia and the dentate nucleus of cerebellum which was suggestive of fahr's syndrome.

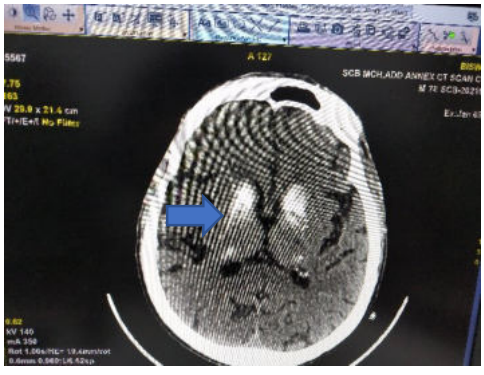

Fig 1: - Bilaterally Symmetrical calcifications involving the basal ganglia

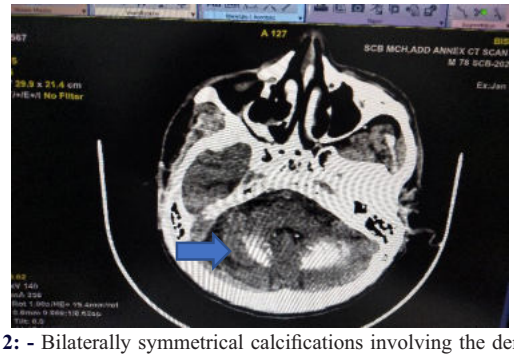

Fig 2: - Bilaterally symmetrical calcifications involving the dentate nucleus of cerebellum

To rule out secondary causes of basal ganglia calcifications further evaluation was done which are as depicted below: -

Table 1: - Important laboratory investigations

Parameter	Laboratory Value	Normal Value
S. Calcium (Ionized)	**0.84 mmol/L**	1 – 1.30 mmol/L
S. Magnesium	2.2 mg/dL	1.8 – 2.6 mg/dL
S. Phosphate	**6.4 mg/dL**	2.5 – 5 mg/dL
S PTH	**130 pg/mL**	10 – 45 pg/mL
S Vit D	22 ng/mL	25 – 50 ng/mL
S. ALP	84 U/L	20 – 140 U/L
TSH	1.2 uIU/mL	0.4 – 5.5 uIU/mL

Thyroid profile was normal. Lumbar Puncture was done to rule out infections but reports were normal. EEG was normal. The findings of hyperphosphatemia, hypocalcemia and raised PTH were suggestive of pseudohypoparathyroidism (PHP). As patient had no features of AHO so PHP type Ia and Ic were ruled out. However due to lack of resources urinary c-AMP response to PTH (Elisworth-Howard test) and Gs-α subunit assay couldn't be done hence differentiation between PHP Ib and PHP II couldn't be done.

Based on the clinical, radiological and laboratory findings a final diagnosis of Fahr's syndrome secondary to pseudohypoparathyroidism was made.

Patient was given T. Levodopa + carbidopa (100/25) for tremors along with calcium and vit D supplementation and supportive treatment with which he had clinical improvement.

DISCUSSION

Fahr's syndrome is a rare disease entity which is characterized by progressive intracranial brain calcifications involving the basal ganglia, cerebellum, cerebral cortex etc. The exact prevalence of fahr's syndrome is not known but on routine radiological examinations an incidence of basal ganglia calcifications of 0.3% - 1.2% have been reported [6]. In one study, 7040 patients were examined with CT scans, out of which 72(10.02%) showed bilaterally symmetrical calcifications [6]. In another study, out of 6,348 CT scans that were reviewed 39 (0.49%) had Fahr's syndrome as the confirmed diagnosis [7].

Fahr's syndrome can be primary/idiopathic which is inherited as autosomal dominant inheritance. A strong genetic link has been suggested. SLC20A2 on chromosome 8p11.2 and PDGFRB on chromosome 5q32, another locus in chromosome 14q are commonly implicated genetic mutations, though other gene may also be associated [3,8].

In contrast, the secondary variant ie: Fahr's syndrome can occur in association with many other conditions mainly disorders associated with calcium-phosphate metabolism like endocrinopathies among which hypoparathyroidism (primary/secondary), pseudohypoparathyroidism, pseudo pseudo-hypoparathyroidism is more common. In a study it was found that Fahr's syndrome occurred in 20 (21.5%) of 93 patients with idiopathic hypoparathyroidism and 26 (42.6%) of 61 patients with pseudohypoparathyroidism [10]. Other conditions associated with fahr's syndrome are infections (rubella, toxoplasmosis, CMV), mitochondrial myopathy, Vit D disorder, Kenny Caffey syndrome type 1, Cockayne syndrome etc. [1].

The exact pathogenic mechanism of fahr's syndrome is not known. At the molecular level, calcification starts within the vascular wall and progressing to the perivascular space and then to the neurons. The mineral deposits may be due to abnormal metabolism of calcium and phosphorous. The deposits are composed of mineral compound like calcium phosphate, calcium carbonate, glyconate, mucopolysaccharide etc. Metals like Fe, Cu, Mg, Zn, Al, Ag and Co can also be found [1, 9].

Clinically Fahr's syndrome can present with a wide variety of neurological and neuropsychiatric signs and symptoms. The usual age of presentation is 3rd to 4th decade of life However, our patient had late onset of disease at 7th decade. In the "Fahr's Disease Registry" the most common clinical manifestation are movement disorders (55%). Among this parkinsonism was seen in 57% cases, chorea in 19%, tremor in 8%, dystonia in 8%, athetosis in 5% and orofacial dyskinesia in 3% cases. Cognitive impairment was the next most common followed by cerebellar involvement and speech disorders. In our case, the patient presented with progressive cognitive decline, tremors and other parkinsonian features. Other manifestations include psychosis, gait disturbances, sensory changes etc. [4].

Pseudohypoparathyroidism (PHP) includes a heterogenous group of endocrinological disorders which is characterized by target organ resistance or unresponsiveness to the action of parathyroid hormone (PTH) mainly though it also extends to include other hormones like thyroid hormone [6]. The estimated prevalence is 0.3 to 1.1 cases per 100000 population based on the geographic location [10]. PHP is divided into type I and type II. Type II is further subclassified as type 1a, type 1b and 1c. Types 1a and 1c have AHO (Albright hereditary osteodystrophy) phenotype with PTH resistance while 1b has isolated resistance to PTH in the kidney with normal PTH response in the bone without AHO phenotype. Type 1a has reduced Gsa subunit activity while type 1c has normal Gsa activity [6].

Diagnosis of fahr's syndrome is based on radiological examination and demonstration of characteristic calcification pattern in the presence of classical neurological signs and symptoms. To rule out secondary causes other investigations to be done for example: - blood and urine for analysis for calcium, phosphorous metabolism disorders, serum levels of PTH, vit D, ALP, calcitonin, Elisworth Howard test, serum creatinine, CSF analysis for infectious etiology etc. If no secondary causes could be found than genetic testing for SLC20A2 sequencing can be considered [1].

There is no definitive treatment for Fahr's syndrome. Treatment is symptomatic. Pharmacotherapy can be used to improve anxiety, depression and to alleviate dystonia. Correction of calcium and phosphate levels can help in relieving symptoms of seizures and movement disorders.

CONCLUSION

Fahr's syndrome is a rare neurodegenerative disorder that can have wide and variable clinical presentation. Fahr's syndrome should be considered as a differential in patients with typical neurologic and neuropsychiatric manifestations and brain calcification in radiology. Accurate diagnosis may be challenging. Thorough search for metabolic and endocrine disorders must be done to ascertain the cause. Patients who are at risk for example those having family history should be screened for at an early stage. Also, genetic counselling for at risk population before conception should be done. A multi-disciplinary approach and a team work including neurologist and psychiatrist is needed for the management of these disorder. Further studies are required to better understand the pathophysiology of the disease and to explore newer treatment modalities for better management of the disease.

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