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Pathology

FAHR'S SYNROME- A RARITY

Dr. Swathi. T*	Postgraduate (MD) Pathology 2nd Year. Osmania Medical College, Hyderabad. *Corresponding Author
Dr. Naga Kalyani Pathuri	Associate Professor, Pathology. Osmania Medical College, Hyderabad.
Dr. S. Vandhana	Assistant Professor, Pathology. Osmania Medical College, Hyderabad.
Dr. K. Swarajya Kumari	Professor, Pathology Osmania Medical College, Hyderabad.
Dr. G.J.Vani Padmaja	Professor And Hod. Department Of Pathology Osmania Medical College, Hyderabad.

ABSTRACT Fahr's disease/syndrome is a rare neurodegenerative disease characterized by symmetrical and bilateral calcification of the basal ganglia. Calcifications are also seen in other areas such as thalamus, dentate nucleus and cerebral cortex. Both familial and non-familial cases of Fahr's disease have been reported, predominently with autosomal-dominant pattern. It has a wide range of clinical manifestations. Diagnosis criteria and checklist have been helpful in diagnosis and differentiation of Fahr's syndrome and Fahr's disease. No specific treatment is available and the management of the patient is mainly symptomatic. Here we present a case report of a 12 year female child presented with Pancytopenia for evaluation with already diagnosed Fahrs disease.

KEYWORDS : Fahr's syndrome, Fahr's disease, Basal ganglia calcification

INTRODUCTION:

Fahr's Disease /Syndrome is a rare, genetically dominant, inherited neurological disorder characterized by abnormal deposits of calcium in areas of the brain that control movement, including the basal ganglia and the cerebral cortex.[1]

It was first reported in 1930 by Karl Theodor Fahr[2]. The term Fahr's disease is used when primary familial brain calcification is present, and the term Fahr's syndrome is used for secondary causes[6,11].Now the term Primary Familial Brain Calcification[PFBC] is preferred for Fahr's disease[9]. It is an inherited or sporadic neurological disorder with a prevalence of <1/1,000,000[2].However, Fahrs disease is thought to be under-recognised because of insufficient investigation of other family members of individuals presenting with brain calcification[9].

CASE REPORT

A 12year old female child, first born child out of 4 [2 female and 1 male sibling] from a non-consanguineous marriage, resident of Adilabad district,Telangana,was referred to Osmania General Hospital, Hyderabad for evaluation of Pancytopenia. H/O Fever, Generalized weakness, loose stools since 1 week. The child was treated symptomatically and multiple units of packed cell and platelet transfusions were done. The below investigations and consultations from various specialists were obtained.

Table1: The below list of blood investigations were done, mentioned below the dates and the blood counts were found to be increased after the transfusions.

Investigations	Outside Inv.	26-Jan	27-Jan	28-Jan	29-Jan	2-Feb	4-Feb
Hb(gm/dl)	6.3	8.7	10	7	11.5	8	
WBC	3400	4600	6200	3900	6000	4200	
N		39.9	58	21	49	68	
L		49.8	37	67	45	28	
M		6.8	3	1	3	2	
E		2.9	2	1	2	2	
B		0.6	0		1	0	
Platelets	7000	5000	Dec.	20000	25000	120000	
CUE			WNL				
RBS			111				
B/Urea(mg/dl)		9.2	7				
S/creatinine		0.37	0.53			0.61	
malaria			neg				
widal				neg			
TSB			0.56				
Direct			0.16				
Total protein			4.78				
Albumin			1.61				
ALPO4(U/L)			438.58				340.18
ALT			50.17				
S. Na		134.8	135.8			143.5	
S.K		6.32	3.78			3.8	
S.Cl		103.7	106				
HIV			NR				
HbSAg			NR				
HCV			NR				
Blood group			A+ve				
T3						1.03	
T4						5.1	
TSH						1.88	
S.Ca(mg/dl)						7.92	6.9
S.Phos(mg/dl)						4.8	4.4
PTH							42.14

Vitamin-D levels-10.15 ng/ml

Bone marrow aspiration was done from iliac crest revealed hypoplastic marrow.[Figure 1]

BONE MARROW ASPIRATION SMEARS

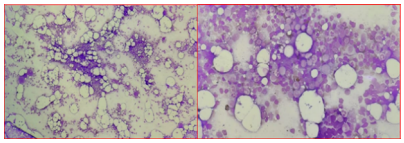

FIGURE1[A]4x;1[B]40x: [Leishman] Hypocellular smear with increased myeloid:erythroid ratio, suppressed erythropoietic series with dyserythropoiesis.

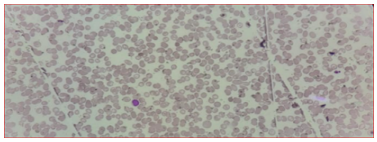

Figure 2:[10x][leishman] Peripheral Smear Shows Decreased Platelets And Wbc.

USG Abdomen-No abnormality was detected.
USG Neck-Evidence of few sub-centimetric lymph nodes within IA, left II, III, IV with preserved fat.

Ophthalmologist opinion- Bilateral Mature Juvenile cataract [Figure 3] with no fundal view. Was advised surgery after improvement of general condition and fitness for surgery has been obtained.

Figure 3: B/L Mature Cataract

Neurologist opinion- change of medication from oral Eptoin to oral Levipil. Endocrinologist opinion was asked for.

Cardiologist opinion- 2-D echocardiography was done- Report – OS ASD = 0.8mm; Left to right shunt; Severe PS.

The patient had complaints of Against Medical Advice.

Past History:
The patient had complaints of H/O Myalgia since past 5 years and chronic Headaches.

H/O B/L Acquired Lenticular Cataract [Figure 3] since the past 4 years. k/c/o Epilepsy [non-GTCS type] on Tab.Eptoin 100mg since the age of 3 years. Episodes of weakness of right upper limb lasting for 15 mins for past 1 year.

Provisional Diagnosis of Fahrs disease on radiological findings was considered 1 year ago.

k/c/o severe Pulmonary Stenosis,ASD since the past 5 years.

2D ECHO—
Severe valvular pulmonic stenosis, PS gradient-90mmHg; small OS-ASD with L-R shunt,RVH, normal size chamber, normal biventricular function,no PAH.

CT Scan-
Symmetric dense calcifications noted in B/L basal ganglia, thalami, dentate nuclei of cerebellum.

Symmetric curvilinear calcifications in B/L frontal,parietal and temporal white mater of B/L cerebral hemispheres.

A small focus of calcification in the pons.
[Figure 4A] multiple calcifications noted in B/L caudate, basal ganglia, thalami, periventricular white mater and dentate nuclei- s/o Fahrs disease.

CT Brain Angiography—[figure 4b]
Diffuse calcification in B/L basal ganglia,thalami, B/Lfronto-parietal sub cortical white mater,pons, dentate nuclei- Fahrs disease.

Left ICA-60-70% Narrowing; Right ICA-60-70% narrowingexcept for 7mm from its origin.

Normal caliber of middle,anterior and posterior cerebral arteries.

CT Brain And Angiography

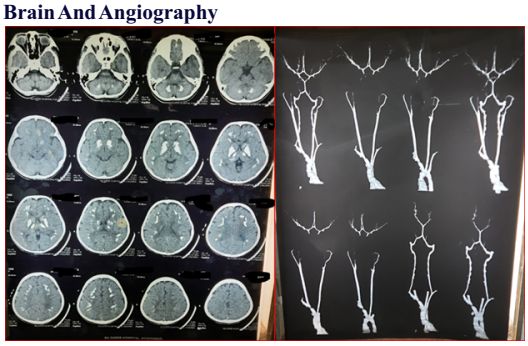

Figure4[A]&4[B]

Rest of the past blood investigations and work up was normal.
PTH-43.5pg/ml
Toxoplasma Gondi- IgG- Neg; IgM- Neg
Rubella IgG- equivocal; IgM- Neg
CMV-IgG-Positive; IgM-Neg
HSV-IgG-Positive; IgM-Neg

Birth History And Childhood: Born as the first child – full term normal vaginal delivery, attained all her milestones at appropriate time for her age.

Diagnosed with epilepsy at the age of 3yrs focal-?, non-GTCS type.

The child was enrolled in school, never involved in any physical activities like running or playing at school as was having dyspnea on exertion. The child had to drop out of school after her vision was found to be decreased.

Physical Examination: The child appeared to be of height appropriate for age, weight 25kgs, malnourished, pallor present, no icterus or pedal oedema. B/L cataract was observed[Figure 3]. Healed scarred lesions of cutaneous infection were noticed on the face of the child.

Her general condition otherwise was maintained, the child was conscious, coherent. All other organ system examination revealed no clinically significant findings.

Family History: No relevant significant family history. Neither of the parents/grandparents nor the siblings had any complaints of epilepsy. Any history of early deaths in the first and second degree relatives or unexplained deaths was asked for and was found negative.

Clinical Diagnosis: Based on the History, Clinical presentation and Radiological findings the diagnosis of Fahrs disease was made.

DISCUSSION:
Synonyms:[2]
Fahr's disease, Fahr's syndrome, idiopathic basal ganglia calcification[7], striopallidodentate calcification[7] and calcinosis nucleorum[7] ;FIBGC[10]; Bilateral striopallidodentate calcinosis[10]; BSPDC; Cerebral calcification nonarteriosclerotic idiopathic adult-onset[10]; Striopallidodentate calcinosis autosomal dominant adult-onset[10]; Ferrocalcinosis[10], cerebrovascular; Fahr disease, familial ; Primary familial brain calcification; Familial idiopathic basal ganglia calcification.

Age of onset is typically in the 40s or 50s,[1] although it can occur at any time in childhood or adolescence.[1]

Etiology of this syndrome is not atributed to any specific cause but is found to be associated with a number of conditions; most common of which are endocrine disorders, mitochondrial myopathies, dermatological abnormalities and infectious diseases[2].

Symptoms of the disorder may include deterioration of motor function, dementia, seizures, headache, dysarthria (poorly articulated speech), spasticity (stiffness of the limbs) and spastic paralysis, eye impairments, and athetosis (involuntary, writhing movements)[1].

It can also include symptoms characteristic of Parkinson's disease[2,3] such as tremors, muscle rigidity, a mask-like facial appearance, shuffling gait, and a "pill-rolling" motion of the fingers[1]. These symptoms generally occur later in the development of the disease. More common symptoms include dystonia (disordered muscle tone) and chorea (involuntary, rapid, jerky movements)[1].

Calcified deposits found in brain are **made up** of calcium carbonate and calcium phosphate[2,7], and are commonly located in the Basal Ganglia, Thalamus, Hippocampus, Cerebral cortex, Cerebellar Subcortical white matter and Dentate Nucleus[2,7]. In the pathologic examination of Fahr's syndrome, calcium deposits were present in extracellular or extravascular space, especially around the capillaries[3]. However, it is not clear whether abnormal calcium deposition in the brain is caused by the local destruction of the blood brain barrier or by calcium metabolic disorder of neurons[3].

Imaging modalities for the diagnosis include CT, MRI, and plain radiography of skull[2]. Other investigations include blood and urine testing for hematologic and biochemical indices[2].

Genetics:
Mutations in

SLC20A2(solute carrier family 20 member 2).
PDGFRB(platelet derived growth factor receptor beta).
PDGFB(platelet derived growth factor beta), and recently,
XPR1(xenotropic and polytropic retrovius receptor 1).[11]
MYORG(myogenic regulating glycosilase)[11] have been identified.

Sequencing of **SLC20A2** should be undertaken first. If no mutation is identified, deletion/duplication analysis of SLC20A2 can be deliberated[2].

Differential Diagnosis:[2,11]
Calcification of the basal ganglia can occur in a number of familial and non-familial conditions.

Symmetrical Basal ganglia, caudate nucleus, periventricular calcifications on radiological investigations favor the diagnosis Fahrs disease/syndrome.

The term Fahr's disease is used when primary familial brain calcification is present, and the term Fahr's syndrome is used for secondary causes.

Genetic mutations can be the cause for Fahrs disease.

Secondary causes include metabolic/endocrine disorders associated with calcium and parathyroid hormone level abnormalities or infectious causes like Brucellosis, AIDS, Toxoplasmosis and TORCH Complex or toxic exposure to carbonmonoxide or lead or SLE like condition.

- Congenital or early onset along with intellectual disability or systemic involvement if present, then alternate diagnosis should be considered.
- If Basal ganglia calcification and ophthalmologic abnormalities are seen in infancy- infectious disease etiology should be looked for.
- Latent Tetany and myopathic changes along with changes in somatosensory, visual and brain stem auditory responses, then parathyroid dysfunction, mitochondrial disease or other disease associated with brain calcification may be considered.

Normal serum calcium,phosphorous and parathormone levels have ruled out endocrine abnormality like Hypoparathyroidism, Pseudohypoparathyroidism, Idiopathic/Secondary Pseudohypopara thyroidism.

Negative family history and normal siblings of the child have ruled out mitochondrial diseases and familial cause of basal ganglia calcification.

Genetic analysis for the SLC20A2, PDGFRB gene mutations, the most common mutations found in Fahr's or whole genome sequencing would help in analyzing mutations in any other genes associated with syndromes associated with basal ganglia calcifications.

Early onset of symptoms along with eye manifestations, Cardiovascular system findings, Hypoplastic marrow and serological evidence of IgG positive for CMV,HSV and equivocal for Rubella favor the infectious etiology.

Treatment/ Management:
If Fahr's disease-
No specific remediation; only symptomatic therapies.

If Fahr's syndrome-
Treatment should be directed at the specific pathology, with symptomatic therapy adjunctively.

Disease is as yet incurable but management and treatment strategies mainly focus on symptomatic relief[1,2,7] and eradication of causative factors[2].

CONCLUSION:
Fahr's disease/syndrome is rare neurological disease manifested by basal ganglia calcifications. Here we have presented a case suspected as Fahrs disease on CT scan which remains a gold standard in evaluating the extent of calcifications. Normal serum levels of calcium and parathyroid hormone have ruled out the metabolic causes. Negative family history has ruled out familial causes. Early age of presentation with Cataracts, CVS abnormalities, Hypoplastic marrow, Positive serology for TORCH Complex helped us in concluding the case as Fahr's syndrome secondary to infectious etiology.

Consent:
The consent for sharing the patient case record, investigations and the images was taken. Due care has been taken to maintain the confidentiality and to conceal the identity of the patient.

The Approval for this study has been obtained from the Institutional Ethics Committee of Osmania Medical College, Hyderabad, Telangana.

Conflict Of Interest: There is no conflict of interest.

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