Mineral Deposition in Brain Due to Endocrine Disorder - Fahr's syndrome - A case report

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Abstract: *Fahr's* syndrome is a rare neurological disorder characterized by abnormal calcifications in the brain [Basal ganglia- involves in tuning voluntary movements,Cerebral cortex- involves in maintaining attention,Thalamus- involves in relaying motor and sensory signals to the cerebral cortex and refutes sleep,wakefulness, and Hippocampus - involves in storing long term memories, Cerebellar white matter-helps in communication between the grey matter regions and rest of the body and dentate nucleus involves in motor and nonmotor function]. This is mainly causedby genetic mutations, other diseases such as endocrine disorders, infections, and others. Clinical manifestations include movement disorders and Neuropsychiatric related symptoms. Diagnosis of Fahr's syndromecan be done by neuroimaging tests (CT scan and MRI), Parathyroid dysfunction (PTH levels), progressive neurological dysfunction, mitochondrial disease, family history, or other disease associated with brain calcificationare alsoconsidered. There isno cure for Fahr's syndrome, but only symptomatic treatment is given, if calcium and phosphate levels are abnormal, they can be prescribed with intravenous calcium gluconate and oral therapy with calcium and calcitriol. Antiepileptic drugs for seizures, headaches, and tremors Alendronate drug was beneficial. Here we are reporting a case of a 12-year-old female with chief complaints of tonic-clonic seizures, vomitings, tetany which was diagnosed as Fahr's Syndrome secondary to Pseudohypoparathyroidism based on MRI where bilateral calcification was observed in basal ganglia and based on parathormone, calcium andphosphate levels.

Keywords: Fahr's disease, Pseudohypoparathyroidism, Parathormone, basal ganglia.

Introduction

Fahr'ssyndrome is calcification in basal ganglia, a rare inherited or sporadic neurological disorder. A German Neurologist *Karl TheodorFahr* first describe brain calcification [(1)]. But before him in 1850 Delacour described the presence of vascular calcifications in basal ganglia [(2)]. Then in 1855, Bamberger described the

histopathological entity of calcifications in thinner blood vessels [3]. Over the years different names associated with this condition [4]. Recently the term syndrome has been suggested when the secondary and potentially treatable cause is found especially in endocrine problems in which abnormal calcium phosphate ratio is found [5,6]. In Fahr's syndrome calcified deposits are seen in basal ganglia, cerebral cortex, thalamus, hippocampus, cerebellar subcortical white matter and dentate nucleus, these calcified deposits are made up of calcium carbonate and calcium phosphate. This Fahr's disease commonly affects young to middle-aged adultsand may be due to hormonal imbalance and genetic abnormality. Most cases of Fahr's Syndrome present with seizures and extrapyramidal symptoms first, then they may have Cerebellar dysfunction, dementia, neuropsychiatric symptoms, and speech difficulty [7]. To identify possible biochemical abnormalities, and other causes which result in calcium deposition an etiological classification has been proposed that is Primary form which includesgenetic cause - autosomal dominant, familial, and Sporadic forms [8]. And also passed as an autosomal recessive trait [5],[6]. Secondaryforms associated with different diseases (endocrine disorder-Pseudohypoparathyroidism, idiopathic or Secondary hypoparathyroidism, toxic exposure like lead and carbon monoxide, calcium phosphorus abnormalities disimmunopathies (SLE), infections-Brucellosis, AIDS, toxoplasmosis, TORCH complex[9]. In primary forms metabolic(pseudohypoparathyroidism,hypoparathyroidism)and other secondary causes(Toxoplasmosis,TORCH complex, HIV,etc) are absent which means it includes only the genetic abnormality. Sporadic forms may be due to denovo mutations or to a mutation transmitted by an asymptomatic undiagnosed parent[10],[11].

Pathogenesis

In adults and infants, pathological features are similar and not affected by age. Firstly calcification starts within the vessel wall and perivascular space and then ultimately extends to the neurons. Progressive basal ganglia mineralization compresses vessel lumen and causes impaired blood flow, neural tissue injury, and deposition of minerals [12,13]. The mineral composition of the calcification varies with the anatomical site. It may be due to abnormal metabolism of calcium and phosphorus but some reports contradict these findings [14,15,16,]. Most calcifications occur symmetrically, and bilaterally and few occur unilaterally. In some review articles, it was deduced that there are no abnormalities in calcium metabolism denying the pathophysiological significance of concurrent altered calcium metabolism [17]. Calcifications occur commonlyin basal ganglia, thalamus, hippocampus, cerebral cortex, and subcortical white matter [1], these calcium deposits along with calcium carbonate and calcium phosphate also composed of metals including iron, copper magnesium, zinc, cobalt, silver, and aluminum, also gluconate, mucopolysaccharides were found [18,19]

Case report

Case report of a female patient of age 12-year-old was admitted to hospital with chief complaints of seizure activity for 2 episodes. 1st - Episode duration is 20 minutes with tonic-clonic movements of both upper limbs and lower limb, with deviation neck, frothing, sudden fall, uprolling of eyes andwith loss of consciousness, urinary incontinence also present, and postictal drowsiness present for 3 hours. 2nd Episode duration for 5

minutes, no frothing, no loss of consciousness, no uprolling of eyes, no deviation of the neck, only vomiting 10-15times contains food particles. History of using Antiepileptic drugs for 3 days. (T. levipil 20 mg / kg / day, Syp. Calcitriol- God). She was positive with B/L Trousseau sign and tetany. Laboratory findings include at calcium 4.58 (8.6 - 10.2 mmol/L) and phosphorus –8.2 (2.5 - 4.5mg/dl). PTH levels- 260-ng/L. Above findings with MRI Scan- (BL basal ganglia calcification) toconcluded as Fahr's syndrome. Secondary to Pseudohypoparathyroidism and she was prescribed with Inj. Midazolam –25cc /iv /sos, Inj zofer- 1cc / iv / OD, syp calcitriol-10ml / TID, T. calcium p / o. Next day T. Levipil 500mg -BID was given. On 3rd day T. Levipil holder a d Inj.Levipil -10mg/kg was given. On the 4th day T. Levipil is prescribed by stopping Inj.Levipil. On the 5th day Inj. Levipil gave onholding tablet by continuing other drugs.

Discussion-

Calcification in Fahr's syndrome occurs in basal ganglia, cerebral cortex, thalamus, hippocampus, cerebellar subcortical white matter, and Dentate Nucleus. This calcification occurs due to genetically or due to other diseases [8,9,10,11]. In this case, the etiology of brain calcifications is known by PTH levels and calcium-phosphorus ratio, that is in Pseudohypoparathyroidism PTH levels are increased and calcium levels get decreased, phosphorus levels are also increased. These calcium phosphorus abnormalities due to PTH disorders are the most common etiology for calcification [20]. The principal function of PTH is the maintenance of plasmatic levels of calcium by withdrawing calcium from bone and reabsorbing it from Glomerular filtrate and it indirectly increases intestinal absorption by stimulating the active vitamin D production [3], Parathormone helps in increasing the phosphorus excretion in urine and bicarbonates excretion also[22]. High phosphate levels for a longer duration can lead to phosphate transporter down-regulation in basal ganglia which causes colloid precipitate cerebral blood vessels and brain calcification. In this case, the secondary cause is Pseudohypoparathyroidism linked to the primary cause that in this condition brain calcification occurs due to resistance to parathormone. This resistance (secondary cause) had been linked with mutations (primary cause) in GNAS (Guanine nucleotide-binding protein G alpha stimulating) and STXT6 Syntaxin causing seizures, and movement disorders with or without cognitive impairment. Along with this mutation in the gene encoding, type3 sodium-dependent phosphate transporter2 (SLC20A2) located on chromosome 8 has also been reported as the genetic basis for the pathophysiology of Fahr's disease.

Recently mutations in four different genes SLC20A2, PDGFRB, PDGFB, and XPR1 were identified along with novel mutations in the myogenic regulating glycosylase gene which cause movement disorders, cognitive decline, and psychiatric symptoms [23].SLC2OA2

involved in making sodium-dependent phosphate transporter 2 by providing instructions and helping in maintaining phosphate homeostasis, PDGFRB (5q32) and PDGFB (22q131) are involved in the recruitment of pericytes, blood-brain barrier regulation, and angiogenesis [24, 25]. XPR1(1q25.3) gene helps in phosphate export function and helps in phosphate homeostasis [26].

Symptoms due to hypocalcemia include paraesthesia, cramps, Spasms of carpal and pedal muscles, seizures, neuromuscular irritability, ECG abnormalities like prolonged QT interval, neurological signs like seizures, loss of consciousness, and postural instability[27]. Other causes of Fahr's syndrome are brucellosis, AIDS, toxoplasmosis, torch Complex, toxic exposure (lead and carbon monoxide), and disimunopathies. Cockayne syndrome, goutieres Syndrome, mitochondrial disease (MELAS, MERF), cots syndrome, Neuro ferritinopathy, and NBIA also cause brain calcification. Generally for the treatment of Fahr's syndrome symptomatic treatment is given, Because there is no cure to treat Fahr's syndrome only management and treatment strategies focus on symptomatic relief. Selective removal of deposited calcium from the brain without affecting bone calcium and other tissue is impossible tank [26]. For parathyroid dysfunction *iv* calcium gluconate or long-term oral therapy with calcium and calcitriol can decrease the symptoms [28]. Antiepileptic drugs for seizures, mood stabilizers, and antipsychotic drugs for psychiatric features. Bisphosphonates when released from an active osteoclast help in preserving the calcium and phosphate levels within the bone by decreasing bone resorption. Drugs belonging to this bisphosphonate group like Disodium Etidronate, and Alendronate helps decrease bone resorption and help maintain the calcium, and phosphate homeostasis within the bone. In this pseudohypoparathyroidism condition, this bisphosphonate group of drugs helps in symptomatic relief like headache, seizures, gait, and ataxia but does not alter the quantity of calcification. (11)

Conclusion

In this case, Pseudohypoparathyroidism is the main etiological factor. So patients who are suffering from focal and generalized seizures it is necessary to test Parathyroid function, and calcium-phosphorus levels to avoid complications like Fahr's syndrome.

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Conflict Of Interest

The author declared no conflict of interest

ABBREVIATIONS

SLC20A2: Sodium Dependent Phosphate Transporter 2,

PDGFRB: Platelet Derived Growth Factor Receptor beta,

PDGFB : Platelet Derived Growth Factor Subunit B,

XPR1: Xenotropic Polytropic Retrovirus Receptor,

TORCH COMPLEX: Toxoplasmosis, Rubella, Cytomegalovirus, Heroes Simplex, and HIV.

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