

Review

Anesthetic Considerations in a Case of Fahr and Primrose Syndrome

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ABSTRACT

In this review article, brief description, concerns, anesthetic management and perioperative care patients with Fahr syndrome and Primrose syndrome has been made. There is a paucity of literature with respect to management of such cases. There are limited case reports reported in the literature. The literature search has been made by using Google scholar, PubMed, Medline, Medscape and other search-related search engines with the following keywords.

Keywords

Fahr syndrome; Primrose syndrome; Anesthesia; Calcium.

Abbreviations

ALP: Alkaline Phosphatase; CSF: Cerebrospinal Fluid; MELAS: Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke; ECG: Electrocardiogram; NK: Natural killer; GP: Globus Pallidus; PTH: Parathyroid Hormone; cAMP: Cyclic Adenosine Monophosphate; TIVA: Total Intravenous Anesthesia.

INTRODUCTION

Fahr Syndrome

Fahr syndrome or Fahr disease is a rare inherited or sporadic neurological disorder. The prevalence of such disorder is <1/1,000,000 and is characterized by basal ganglia calcification. It was originally described by Karl Theodor Fahr and is characterized by abnormal deposits of calcium in brain areas that control the movement of the body. Involved areas of the brain include basal ganglia, thalamus, dentate nucleus, cerebral cortex, cerebellum, hippocampus and subcortical white matter. Initially, patients

present with extra-pyramidal symptoms, cerebellar dysfunction, speech dysfunction, and dementia and later on with neuropsychiatric symptoms. It is most commonly transmitted as an autosomal dominant trait but can also be transmitted as autosomal recessive or sporadically. It involves adult population in the 3rd to 5th decade and locus at 14q (*IBGC1* gene) has been suggested to be commonly involved.¹

Diagnostic criteria for Fahr's syndrome derived from Moskowitz et al and modified by Manyam et al in 2005 include (Table 1).

Table 1. Diagnostic Criteria of Fahr Syndrome

1. Bilateral calcification of basal ganglia as visualized by neuroimaging, although other parts of brain may also be involved
2. Progressive neurological dysfunction, characterized by movement disorder and neuropsychiatric manifestations. Age of onset is 4th and 5th decade, although may also manifest in childhood as well.
3. Biochemical abnormalities are absent and somatic features are suggestive of mitochondrial or metabolic or other systemic disorder
4. There is absence of infectious, toxic or traumatic cause
5. Family history is consistent with autosomal dominant inheritance.

Differential diagnosis

- Symmetrical basal ganglia calcification can also be seen in variety of other familial and non-familial conditions, which should be taken into account of differentials.
- Usually congenital or early onset along with impairment of intelligence should be worked up for other alternative possibilities or diagnosis.
- Basal ganglia calcification associated with ophthalmological manifestation of a child should be investigated for infections.
- If there is presence of latent tetany or myopathy changes associated with changes in visual or somatosensory responses, parathyroid dysfunction, mitochondrial diseases should be ruled out.
- It is differentiated from calcified angiomas, infections, Addison's disease and encephalitis based on severity and characteristic distribution.

Primrose Syndrome

Primrose syndrome was originally described in the year 1982 and very few cases are reported in the literature. Clinical features are characterized by calcification of pinna, large head, autism, intellectual disability, brain calcification, diabetes, and sparse hair, muscle wasting, movement disorders, Parkinsonism, hypothyroidism, distorted facial features and behavioral abnormalities. Most of the cases are sporadic and are caused by a mutation in *ZBTB20* gene. These cases have similar presentation as that of Fahr syndrome, except for associated distorted facial features and endocrine disorders in them.^{2,3}

DIAGNOSTIC METHODS

CT Scan: It is performed to localize the extent of brain calcification. Most commonly involved areas include lenticular nucleus, mostly globus pallidus (GP), cerebellar gyri, brain stem and subcortical grey matter.

MRI: It is used to assess areas of calcification in basal ganglia using T2 image which gives a low-intensity signal. T1 weighted plane either gives a low or high-intensity signals.

Plain X-Ray: Calcified deposits can be seen as clusters symmetrically over sella turcica as punctate densities, while subcortical and cerebellar calcifications appear wavy.

Cerebrospinal fluid analysis: It should be undertaken to rule out infectious etiology and auto-immune disorders. If no other primary cause for brain calcification is found, molecular testing should be undertaken if family history is suggestive of autosomal dominant inheritance. In genetic analysis, sequencing of *SLC20A2* should be undertaken.

Serum concentration: Serum concentration of calcium, magnesium, phosphorus, alkaline phosphatase, parathormone, and calcitonin should be done. Levels of urinary cAMP, serum creatinine, vitamin D3 lactate, osteocalcin, alkaline phosphatase (ALP) should be evaluated at rest followed by after exercise. Natural killer (NK) cells should also be assessed in all suspected cases of Fahr syndrome. Blood sugar, HbA1c, and thyroid function tests should be sought as Primrose syndrome has associated endocrine disorders.

PATHOGENESIS

Fahr syndrome is characterized by pathological fractures. Calcification is known to affect the vessel wall, perivascular spaces, neuroglia and neurons. Progressive basal ganglia calcification compress the lumen of vessels, leading to impairment of blood flow, tissue injury and mineral deposition. It secondarily occurs around a nidus of mucopolysaccharides and other substances due to defective iron transport and production of free radicals ultimately leading to tissue damage.⁴

ETIOLOGY

Etiopathogenesis in Primrose syndrome is characterized by abnormal high amount of calcitonin, a hormone secreted by the thyroid glands to stabilize blood calcium levels, suggesting that thyroid gland releases an abnormal amount of calcitonin resulting in disruption of calcium level homeostasis (Table 2).

CLINICAL FEATURES

Fahr syndrome is associated with various neurological manifestations such as loss of consciousness and seizure, etc. It can be associated with tetany, occasional myoclonus, spasticity, gait disorder, speech impairment, dementia, parkinsonism like symptoms, chorea, athetosis, coma, dystonia, and so on. It has also been reported to be associated with papilledema and pleocytosis on cerebrospinal fluid (CSF) examination. Fahr syndrome is also known to be associated with movement disorders which include unsteady gait, slurred speech, dysarthria, dysphagia, muscle cramps, involuntary

Table 2. The Various Etiologies of Fahr Syndrome Other Than being Idiopathic Include

1. Endocrine disorders-Idiopathic hypoparathyroidism, pseudo-hypoparathyroidism, secondary hypoparathyroidism, hyperparathyroidism, hypothyroidism, hypogonadotropic hypogonadism
2. Systemic diseases-Systemic lupus erythematosus (SLE), scleroderma
3. Neurodegenerative conditions-brain iron accumulation disease, ferritinoneuropathy, polycystic lipomembraneous osteodysplasia, primitive or secondary calcified brain tumors
4. Infectious diseases-Cockyane syndrome Type I and II, intrauterine and perinatal infections, neuro-cysticercosis, HIV, German measles, neuro-brucellosis, small pox encephalitis
5. Early Onset syndrome-Tuberous sclerosis, brucellosis, Coat's Disease.
6. Heavy metal poisoning, hemochromatosis, CO poisoning, treatment with methotrexate or radiotherapy

movement disorders and easy fatigability. There is no association between extensive calcifications and the higher proportion of neurological impairment, rather it has been seen that disease may be more progressive in those with limited calcification. Neuropsychiatric spectrum ranging from impaired intelligence. Dementia, psychosis, depression, schizophrenia may be seen.

Management of Fahr and Primrose Syndrome

Management of these patients is based on symptomatology.

- Management is based on treating anxiety, depression, psychotic behavior, etc.
- Anti-epileptics are given to manage seizure and oxybutynin are prescribed for associated urinary incontinence.
- Early management of hypoparathyroidism can even reverse the disease process, as reported from a 3-year child, by starting treatment of hypoparathyroidism, mental retardation was reversed.
- Correction of calcium, vitamin D3, phosphorus, magnesium levels have been shown to reverse neurological impairment and seizure and movement disorders associated with hypoparathyroidism.
- Atypical antipsychotics and clonazepam have an added advantage in the management of psychosis in Fahr syndrome. It has been suggested that use of carbamazepine and barbiturates can exacerbate gait disorders in these patients, so should be cautiously used.
- Management of hypothyroidism and diabetes is done with Eltroxin and oral hypoglycemic and insulin respectively.

ANESTHETIC MANAGEMENT

Pre-Operative Evaluation

The pre-operative evaluation in patients with Fahr syndrome is based on the functional status of the individual, symptoms of the seizure, gait disorder, myoclonus, speech disorder, dementia, mood disorders, dystonia, parkinsonism, etc. If Fahr syndrome is associated with hypoparathyroidism, it is characterized by cataract, tetany, seizures, dysarthria, soft tissue calcification, pernicious anemia,

dry hair, alopecia, increased intracranial pressure, and dental caries. Fahr syndrome is also known to occur in patients with Kern Sayre syndrome, and consists of triad of external ophthalmoplegia, retinal degeneration and increase in cerebrospinal fluid protein. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome, a type of mitochondrial disorder is also associated with Fahr syndrome and is characterized by myopathy, encephalopathy, lactic acidosis and stroke like syndrome. Tuberosclerosis is characterized by hypermelanotic macules, facial angiofibromas, plaques, intellectual disability, subependymal nodules, seizure, angiomyolipoma in kidney, rhabdomyoma in heart and cerebral hemartomas which may be calcified. Patients may be on multiple medications including anti-epileptics, anti-psychotics, anti-parkinsonism, calcium, multi-vitamins, mood elevators, etc., same should be enquired about. Usually these patients may not respond to levodopa for Parkinsonism symptoms, but respond to risperidone, which is known to diminish psychotic symptoms. Calcium, vitamin D and parathyroid hormone are given to normalize calcium if associated with hypoparathyroidism. In physical examination, general physical examination and systemic examination is done thoroughly. Speech, balance, gait disorders may be present in systemic examination and the same should be noted. Airway examination should also be done thoroughly. Cataract may also be associated. They may have brady/tachyarrhythmia. Chvostek sign and Trousseau sign should be done to rule out hypocalcemia. Control of blood sugars should also be taken in account.

Pre-Operative Investigations

In addition to detailed history and examination, following investigations are required (Table 3).

MONITORING DURING ANESTHESIA

- Routine standard monitoring includes electrocardiogram (ECG), non-invasive blood pressure, end tidal carbon dioxide, and peripheral oxygen saturation.
- Temperature monitoring, and urine output monitoring are frequently required.
- Invasive blood pressure monitoring may be required in cases where there is a risk of major fluid shifts or blood loss.

Table 3. Pre-Operative Investigations

Complete Blood Count	Laboratory investigations usually reveal normal calcium, phosphorus, parathormone, and vitamin D levels. In some patients, there may be severe hypocalcemia, hyperphosphatemia, elevated parathormone levels, normal renal function, and vitamin D levels, which require looking for hypoparathyroidism.
Blood urea and serum electrolytes-including sodium, potassium, calcium, magnesium, and phosphate	
	Diagnosis of primary hypoparathyroidism is confirmed by low parathyroid hormone (PTH) and calcium levels. Secondary hypoparathyroidism is characterized by low PTH and high calcium levels. Pseudo-hypoparathyroidism is a condition of bone and kidneys characterized by the unresponsiveness of receptors to parathyroid hormone, and there are high PTH and low calcium. Thyroid function tests and urinary cyclic adenosine monophosphate (Camp) levels are also asked in limited cases.
X-ray findings	X-ray findings are suggestive of generalized increase bone density, thickened lamina dura and sacroiliac, femoral head and acetabulum soft tissue abnormalities (characterized by intracranial calcification, calcification of spinal and other ligaments, subcutaneous calcifications, ectopic bone formation, ossification of muscle insertion.

- Calcium levels are also frequently monitored during the intra-operative period.
- In patients with compromised cardiovascular or renal functions, additional monitoring such as invasive blood pressure, neuromuscular monitoring and measuring the depth of anesthesia *via* bispectral index may be required and may vary from case to case. Arterial blood gas analysis is also required in specific case scenario.

ANESTHESIA CONSIDERATIONS

Both regional and general anesthesia has been described by authors, although the reported cases are very few. Goals of anesthesia management revolve around managing metabolic disturbances associated with calcium metabolism. These patients are at risk of malignant hyperthermia, therefore dantrolene should be made available.⁴

Clinical Manifestations of Hypocalcemia Include

Neuropsychiatric symptoms such as seizure, anxiety, dementia, mental retardation, emotional symptoms such as anxiety and depression, extrapyramidal symptoms. Irritability as characterized by positive chvostek sign and trousseau sign, paresthesia, circum-oral numbness, myalgia and muscle spasms. Cardiovascular manifestation include hypotension, congestive heart failure, prolonged QT interval, bradycardia, impaired contractility, arrhythmia, QT, ST elevation and T inversion. Respiratory symptoms include laryngospasm, bronchospasm. Muscle weakness may also develop leading to respiratory failure. Other symptoms include diaphoresis, bronchospasm, biliary colic, cataract, steatorrhea, dry coarse skin, dermatitis, gastric achlorhydria.

Other causes of hypocalcemia should also be ruled out which include acute and chronic renal failure, vitamin D deficiency, magnesium deficiency, pancreatitis, sepsis, massive blood transfusion, radiographic contrast, etc.⁵

The decreased serum calcium associated with hypoparathyroidism produces hyper-excitability of nerves and muscle cells by lowering the threshold potential of excitable membranes. Symptoms may vary from mild characterized by muscle spasms, and severe characterized by hypocalcemia tetany, perioral paresthesia, numbness in toes and feet. Life-threatening hypocalcemia manifestation include laryngeal muscle spasm, producing stridor, labored respiration and asphyxia.⁵ Signs of hypocalcemia include:

Chvostek Sign

Characterized by contracture or twitching of ipsilateral facial muscles produced when facial nerve is tapped at the angle.

Trousseau Sign

Is elicited by inflation of blood pressure cuff slightly above systolic blood pressure for few minutes, the resultant ischemia enhances muscle irritability leading to flexion of wrist and thumb, and exten-

sion of fingers known as carpopedal spasm.

Management of Hypocalcemia Include

- They should have ionized calcium levels done to confirm the diagnosis.
- Mild hypocalcemia ie ionized calcium >0.8 mmol/L are asymptomatic and seldom require any treatment.
- In more severe cases of hypocalcemia replacement therapy is essential. In patients in whom ionized calcium is less than 0.5 mmol/L may be associated with life-threatening complications and require intravenous calcium replacement therapy.
- Administration of calcium bolus 100-200 mg of elemental calcium over 10 minutes followed by maintenance infusion of 1-2 mg/kg/h is done. Serum calcium returns within 6-12 hours. Thereafter maintenance infusion is reduced to 0.3-0.5 mg/kg/h. intravenous
- Calcium should ideally be given slowly with ECG monitoring and through a central line as it is irritant to the veins.
- One must also be cautious in giving calcium to a patient who is also receiving digitalis as it may cause digitalis-induced arrhythmia and heart block.
- Once the calcium levels have reached normal, 1-4 g of elemental calcium is given *via* enteral route. Optimal therapy requires frequent monitoring of calcium, magnesium, vitamin D, potassium, and creatinine.
- Patients are supplemented with intravenous and oral calcium and vitamin therapy if serum ionized calcium levels are low. Hyperventilation should be avoided as alkalosis is associated with further hypocalcemia resulting in the seizure which may be masked due to the use of muscle relaxants and become evident at the time of recovery.

GENERAL ANESTHESIA IN FAHR AND PRIMROSE SYNDROME

During anesthesia, there is interplay of several factors which include nutritional status of the patient, disease progression, calcium levels, drugs used in peri-operative period, transfusion of citrated blood, etc. Anesthesiologist should aim to prevent changes in plasma calcium concentration and its effects on various organs. Control of blood sugars and thyroid should be taken into account. Morning blood sugar and electrolyte should be done. Anesthesia management revolves around all the above-mentioned factors. Choice of anesthesia is dictated by patient's general condition, comorbidities, type and duration of surgery, etc. Post-operative bed ventilator should be arranged depending on the associated factors.⁴

PREMEDICATION

Benzodiazepines are preferred sedative and amnesic agents, but one should be careful to use in patients who have altered sensorium, or in respiratory distress. Use of anticholinergic agent such as atropine 0.01-0.02 mg/kg or glycopyrrolate 0.01 mg/kg may be given in patients with low heart rate. Glycopyrrolate may also be reserved in patients with excessive secretions.

INTRAVENOUS DRUGS

Intravenous induction agents are associated with changes in cardiovascular function. It is crucial to avoid hypotension and arrhythmias. A combination of opioid fentanyl 2-3 mg/kg and benzodiazepine midazolam or diazepam 0.25 µg/kg is safe but should be weighed against hemodynamic stability.^{4,5}

Acidosis should be avoided at all times since it is known to increase the fraction of ionized calcium by decreasing the binding of calcium to albumin whereas alkalosis decreases the same, careful attention of pH should, therefore, be maintained at all times. Metabolic acidosis should be corrected with intravenous fluids or bicarbonate. Respiratory acidosis should be prevented and treated with adequate ventilator parameters. Respiratory alkalosis may occur with hyperventilation and may lower the ionized calcium. Hepatomegaly should limit the use of inhalational agents such as halothane. Anticonvulsants may induce the liver enzymes, therefore dosage of drugs metabolized by the same should be taken into consideration. The dosage of neuromuscular blocking agents should be adjusted accordingly. Succinylcholine may be avoided in patients who presents with spastic paraplegia.⁵

In a case report, in which 58-year-old patient a known case of Fahr syndrome was posted for hernia repair, patient was anesthetized with propofol 2 mg/kg, lignocaine 1 mg/kg, fentanyl 2 µg/kg, and rocuronium 0.6 mg/kg, and maintained with 50% O₂ and N₂O in 2% sevoflurane. Twenty milli liter of calcium gluconate was given by titrating with arterial blood analysis and assessing calcium levels. The patient had spontaneous recovery after 4 minutes of stopping inhalational anesthesia. Reversal agents were not required and the patient was extubated uneventfully.⁴

MALIGNANT HYPERTHERMIA

Risk of malignant hyperthermia is found to be increased in Fahr syndrome, as suggested by various case reports.^{3,4,6} It is seen that calcium homeostasis is abnormal in susceptible individuals so that various agents can increase free ionized intracellular calcium concentration. Primary abnormality is related to abnormally sensitive calcium release mechanism. Considering the possibility of malignant hyperthermia, administration of trigger agents must be stopped immediately, and anesthesia is maintained with opioids, sedatives and non-depolarizing muscle relaxants. Vaporizer should be removed from the anesthesia workstation, and patient is hyperventilated with 100% oxygen, other management include administration of dantrolene 2 mg/kg, repeated every 5 minutes until cardio-respiratory stabilization occurs. Dantrolene acts as a specific ryanodine receptor antagonist and inhibits sarcoplasmic reticulum of calcium. Side effects of dantrolene include prolonged breathing difficulty, tissue necrosis, nausea, vomiting, headache, dizziness, etc. One vial of dantrolene contains 20 mg to be dissolved in 60 ml distilled water. Volume resuscitation and vasopressors may be required to maintain hemodynamics. Monitoring of arterial blood gases, serum electrolytes, creatine phosphokinase, myoglobin, lactate levels are required to determine the success of therapy. Forced diuresis and cooling is required to prevent acute renal failure and hyperthermia respectively. The patient should be

transferred to intensive care unit (ICU) for further monitoring. Total intravenous anesthesia (TIVA) can be preferred in such patients as volatile agents increase the susceptibility of malignant hyperthermia.⁷ There is a relative paucity of literature with respect to the incidence of malignant hyperthermia in cases of Fahr and Primrose syndrome, but one must be cautious in predicting the same and managing accordingly. As far as possible, triggering agents should be avoided in them.

LOCAL ANESTHETICS

There have been reports which have suggested that cardiotoxicity of local anesthetic-bupivacaine may be increased in the presence of hypocalcemia. The mechanism of bupivacaine-induced cardiotoxicity is mediated *via* changes in calcium concentration and is mediated *via* inhibition of calcium current through I type calcium channels. It has also been suggested that presence of cardiotoxicity is potentiated in the presence of calcium antagonists. Loco-regional anesthesia is avoided in cases of thrombocytopenia, coagulopathy and bleeding diathesis.

SPINAL ANESTHESIA

There has been a single case report in which patient was given spinal anesthesia for repair of varicocele for non-obstructive azoospermia in a patient with Fahr syndrome. The patient maintained hemodynamic stability and was shifted uneventfully in the recovery room. The patient also voided after 6 hours and motor blockade effect was not prolonged. However, note should be made of an associated thrombocytopenia or coagulopathy in which spinal anesthesia is relatively contraindicated. Spinal anesthesia is also relatively contraindicated in patients with epilepsy, behavioral disorders, with altered sensorium, etc.⁶

Massive Blood Transfusion

When blood is transfused at the rate of 30 ml/kg/h maintaining the hemodynamic stability, compensatory mechanisms ensure that serum calcium is maintained in normal arrange. When the rate of transfusion of blood is rapid, it temporarily decreases the calcium concentration and recovers after the infusion is decreased. But it has been seen that clearance of citrate from the blood may be slowed in the presence of hypothermia. Therefore, rapid transfusion of cold citrate containing blood products results in lowering of serum calcium concentrations. Sudden decrease in calcium concentration results in hypotension that responds transiently to calcium injection. Reduction in blood pressure may be profound in patients with underlying cardiac disease and severely impaired liver and kidney functions. Clearance of citrate from the blood is done by maintaining adequate urine output, maintaining normothermia, and increasing systemic and hepatic blood flow.⁵

RECOVERY

Periodic post-operative monitoring of ionized calcium is recommended. For patients with renal compromise, fluid administration should be based on urine output. For patients with cardiovascular compromise, monitoring should be continued in recovery.

CONCLUSION

For early diagnosis of malignant hyperthermia due to volatile anesthetics and cardiac effect, careful monitoring, invasive blood pressure follow-up and blood gas investigation should be carried out. As personality changes and impairment in mental functions is marked in these syndromes and the etiology of intracerebral calcification cannot be identified, general anesthesia is safer. In these patients, preparations should be made for difficult intubation and care should be taken for the risk of the development of malignant hyperthermia in association with inhaled anesthetics. Metabolic disturbances, most of which are associated with calcium metabolism, are known. In addition, the probability of difficult intubation owing to calcium metabolism disturbance, should be borne in mind.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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