**Abstract**

Homozygous Familial Hypercholesterolaemia is a metabolic disorder which usually presents with early cardiac disease ranging from premature ischaemic heart disease, including myocardial infarction to aortic root stenosis, but rarely it may present with earlier anginal symptoms due to supravalvular aortic stenosis. A 17-year old South Asian boy presented himself with chest pain associated with mild to moderate exercise. He was diagnosed as a case of Homozygous Familial Hypercholesterolaemia. His anginal symptoms were due to an underlying supravalvular aortic stenosis lesion which is a rare presentation of Homozygous Familial Hypercholesterolaemia.

**Keywords:** Homozygous Familial Hypercholesterolaemia, Metabolic disorder, Myocardial infarction, Supravalvular aortic stenosis.

**Introduction**

Familial Hypercholesterolaemia is a genetic disorder which presents with elevated levels of low-density lipoproteins (LDL-C) and total serum cholesterol. The disease occurs due to an underlying genetic defect involving the short arm of chromosome 19. Mutations may result either in complete absence of the LDL receptor, defective binding of LDL to the receptor or defective internalisation and transport of the LDL. There is a gene dose effect; homozygous individuals with two mutated LDL receptor alleles are more frequently and severely affected than heterozygote individuals who have a single mutant allele.\(^1\)

The prevalence of heterozygous form is 1 in 500, with a higher ratio in certain populations. The homozygous form occurs in 1 in million.\(^2\)

Patient with homozygous condition usually presents at an earlier age with signs and symptoms of ischaemic heart disease and peripheral vascular disease.\(^3\) Homozygotes with Familial Hypercholesterolaemia have a higher risk of aortic stenosis due to atherosclerotic involvement of the aortic root or the supravalvular region; but the incidence is relatively lower in heterozygotes.\(^4\) Premature atherosclerosis in Familial Hypercholesterolaemia may affect the aortic root, but involvement of the aortic valve is a peculiar feature if present in a patient with Familial Hypercholesterolaemia.\(^5\)

Premature aortic calcifications may also be present in adults presenting with Familial Hypercholesterolaemia. Individuals having supraventricular aortic stenosis may present with chest pain, syncope, dizziness or clinical features of heart failure.

**Case Presentation**

A 17-year-old male presented in the Out-Patient Department with complaints of chest pain for the preceding six months. He started to experience chest pain while riding a bicycle to work. The pain was severe in intensity, radiated to the jaw and was relieved by rest. There was no history of shortness of breath or cyanosis. He had taken no medicine recently other than Acetoaminophen for his chest pain. There was no illness reported in the previous six months. There was no history of cough, sore throat, flu, diarrhoea, vomiting, allergies or arthralgias. He did not smoke and denied any illicit drug use.

On physical examination, his oral temperature was 98°F, blood pressure 100/60 mm of Hg, respiratory rate 14/min. His pulse was slow-rising, low-volume, regular in rhythm with a rate of 78/minute. There was no pallor or jaundice, and JVP was not raised. There was no clubbing, palmar erythema or palpable nodules. On examination of his hand, xanthomatas were present in interdigital webs on the right hand and had been there since the patient was 6 years old (Figure-1).

Tuberous xanthomatas were present on elbows and knees. There was no pedal oedema and no lesions were seen on his Achilles tendon. Lungs were clear to auscultation. On auscultation of precordium, first and second heart sounds were normal, with ejection systolic click followed by grade 4 early systolic murmur radiating to both carotids which increased in intensity on expiration. Abdominal exam revealed no haematomegaly and splenomegaly. Peripheral pulses were normal.

His Fasting Lipid Profile showed serum cholesterol level 346mg/dl (150mg/dl to 170 mg/dl), LDL level 218
mg/dl (< 130 mg/dl), triglycerides 179 mg/dl (50 mg/dl to 150 mg/dl) and HDL level 56 mg/dl (40-60 mg/dl). EKG showed strain pattern in lateral leads V5 - V6 suggestive of left ventricular hypertrophy. The patient was admitted and scheduled for cardiac imaging studies. Echocardiography showed normal aortic valve with significant narrowing just above the aortic valve with peak gradient of 140 mmHg and mean gradient of 90 mmHg across the stenosis. Mild to moderate concentric left ventricular hypertrophy was also seen with good biventricular systolic function. CT angiogram confirmed the tight supravalvular aortic stenosis with heavy calcification along with patent coronary vessels (Figure-2).

The patient's family was also screened by physical examination and a fasting lipid profile. Both his parents and all his siblings had elevated serum cholesterol levels and serum LDL levels with slightly elevated triglycerides and normal HDL levels. Skin lesions similar to the ones seen in the patient were present in his brother along with murmur of aortic stenosis. Thus on the basis of history, physical examination showing xanthomata, findings of CT angiogram and results of lipid profile of the patient and his family, he was diagnosed as a case of homozygous Familial Hypercholesterolaemia (type II hyperlipoproteinemia) with supravalvular aortic stenosis. Secondary causes such as nephrotic syndrome and hypothyroidism were excluded.

The patient was advised strict diet control. Treatment with simvastatin was started with 20 mg/day initially. Dose was gradually increased to 60 mg/day over a period of 3 months. Baseline liver function tests and creatinine kinase were done before initiation of therapy with statins. Aspirin was prescribed to prevent any thromboembolic event. The patient is currently awaiting aortic root reconstruction surgery to correct his supravalvular aortic stenosis with calcification.

The patient is followed up regularly in the outpatient department and lipid profile is repeated every 3 months. Since his initial visit, his total serum cholesterol has decreased by 20% and his LDL level has decreased by 25%. The goal is to bring down the cholesterol level to less than 200 mg/dl and LDL level to at least below 130 mg/dl which are near optimal values as recommended by ATP III guidelines. This would lead to an improvement in the cholesterol to HDL ratio which is the most important predictor of atherosclerosis.

The patient is monitored for any adverse effects of the drug therapy and liver function tests are scheduled at regular intervals.

Discussion

Familial Hypercholesterolaemia is a genetic disease with hereditary transmission, but it presents with a wide range of phenotypic expressions. The variability is the result of various types of underlying mutation in the LDL receptor gene all of which result in Familial Hypercholesterolaemia. Risk factors such as age, gender, smoking and hypertension also contribute to the clinical signs and symptoms seen in the patient at the time of the onset of the disease.6
The typical manifestation seen in homozygous Familial Hypercholesterolaemia patients are coronary ostial stenosis and aortic root stenosis which occur due to cholesterol deposition in the aortic root at a young age.\(^7\)

Contrary to homozygous Familial Hypercholesterolaemia, in the heterozygous strain the usual age of presentation is highly variable and depends on the molecular defect in the LDL receptor gene. Patients with coexisting cardiac disease risk factors may present at an earlier age with symptoms of cardiovascular disease.

Most common cardiovascular presentation in homozygous Familial Hypercholesterolaemia is premature ischaemic heart disease, but relatively few cases present with earlier anginal symptoms due to atherosclerotic involvement of aortic root or supravalvular aortic stenosis.\(^8\) There should be a high index of clinical suspicion in considering valvular heart disease when chest pain is reported with clinical and laboratory features suggesting homozygous Familial Hypercholesterolaemia in young adults.

An earlier intervention of supravalvular aortic stenosis along with lipid-lowering therapy decreases morbidity and mortality.\(^9\) Guyton JR et al reported in their study that a combination treatment with statin, ezetimibe and extended-release niacin may prove to be more beneficial than any of these drugs used alone.\(^10\) Statin therapy also has the added advantage of improving endothelial dysfunction in Familial Hypercholesterolaemia patients.

Invasive procedures such as lipid apheresis and liver transplant may be a last resort in patients who have no functional LDL receptors and are not responding to pharmacological therapy. Both procedures are expensive and have limited availability. Patients presenting with cardiac symptoms may need CABG or surgery involving the aortic root.

### Conclusion

Supravalvular aortic stenosis should be considered a possible diagnosis in young adults presenting with anginal symptoms with clinical and laboratory features suggestive of homozygous Familial Hypercholesterolaemia. Early diagnosis and intervention may lead to decrease in morbidity and mortality.

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### References