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Short Communication

Familial hypercholesterolemia supravalvular aortic stenosis and extensive atherosclerosis

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ABSTRACT

Familial hypercholesterolemia is an autosomally dominant disorder caused by various mutations in low-density lipoprotein receptor genes. This can lead to premature coronary atherosclerosis and cardiac-related death. The symptoms are more severe in the homozygous type of the disease. Premature malignant atherogenesis leading to aortic root abnormalities causing supravalvular aortic stenosis is rare. Our case demonstrates the diagnostic imaging findings of the phenotype of patients who have severe elevated LDL with familial hypercolesterolemia.

A 36-year-old female presented with complaints of nodular eruptions over extensor surfaces of elbow joint and chest pain on exertion. The patient was diagnosed as suffering from familial hypercholesterolemia. Blood pressure of 160/90 mmHg. On cardiac examination a systolic ejection murmur (Levine III/VI) over right second sternal border with radiation to the neck was present.The patient had tendon xanthoma (15 mm radius) at both elbows and xanthelesma (Fig. 1A, B). The lipid profile showed low density lipoprotein (LDL) −430.0 mg/dl, Triglycerides (TG) −71.0 mg/dl, high density lipoprotein (HDL) −47.0 mg/dl. Her mother and two siblings were not hyperlipidemic. A 12-lead electrocardiogram indicated sinus rhythm of 76 beats/min and left ventricular hypertrophy with strain pattern. Transthoracic echocardiogram identified a mild to moderate supravalvular aortic stenosis with a peak Doppler velocity of 3.2 m/s and an estimated mean pressure gradient of 20 mmHg (Fig. 1C, D). CT calcium score was 1032. Severe calcification was noted in the aortic root and ascending aorta causing supravalvular aortic stenosis (Fig. 1E,F). Also significant calcification and luminal narrowing was present in left common carotid and abdominal aorta beginning from lower border of L1 extending upto bifurcation (Fig. 1G). Bilateral renal arteries were spared. CT coronary angiography showed diffuse triple vessel disease with significant calcified plaques (Fig. 1H).

Premature malignant atherogenesis leading to aortic valve and root abnormalities is a recognized complication of homozygous familial hypercholesterolemia.[1–3] Noninvasive imaging should be done for assessment of hemodynamically severe involvement, which may require surgical intervention.

Although cutaneous xanthomas and aortic valve/root involvement are rarely seen in heterozygotes and typically present with cardiovascular disease in the 30s and 40s, our patient is probably heterozygous. Supravalvular aortic stenosis (AS) is also seen in some genetic diseases such as familial supravalvular AS, a rare (1 in 20,000 live births) dominant condition, and Williams-Beuren syndrome.[4] The diagnosis of Williams syndrome could be ruled out since our patient does not have dysmorphic appearance and had good mental development.

Familial hypercholesterolemia, with a heterozygous disease incidence of 1 in 500, is the most common known monogenic form of inherited metabolic disease. Heterozygous familial hypercholesterolemia patients usually have a twofold increase in total cholesterol and LDL-derived cholesterol and typically present with cardiovascular disease in their 30s and 40s.

Various treatment options are available to manage familial hypercholesterolemia. Dietary treatment alone is unlikely to lower the cholesterol level to an acceptable concentration, however it should be a major part of any long term treatment because it can lead to a lower dose of pharmacologic drugs.[5]

To approach the LDLc goals, a high dose of one of the statins is recommended. One meta analysis showed an overall 32% reduction in LDL cholesterol and 1.9 mmol/L absolute reduction in LDL after treatment with various types of statins in children aged 8–18 years with heterozygous familial hypercholesterolemia. Statins could also increase high density lipoprotein (HDL) by 3.4% but had no significant effect on reduction of triglycerides. Therefore it was concluded that statin monotherapy was safe,well tolerated and

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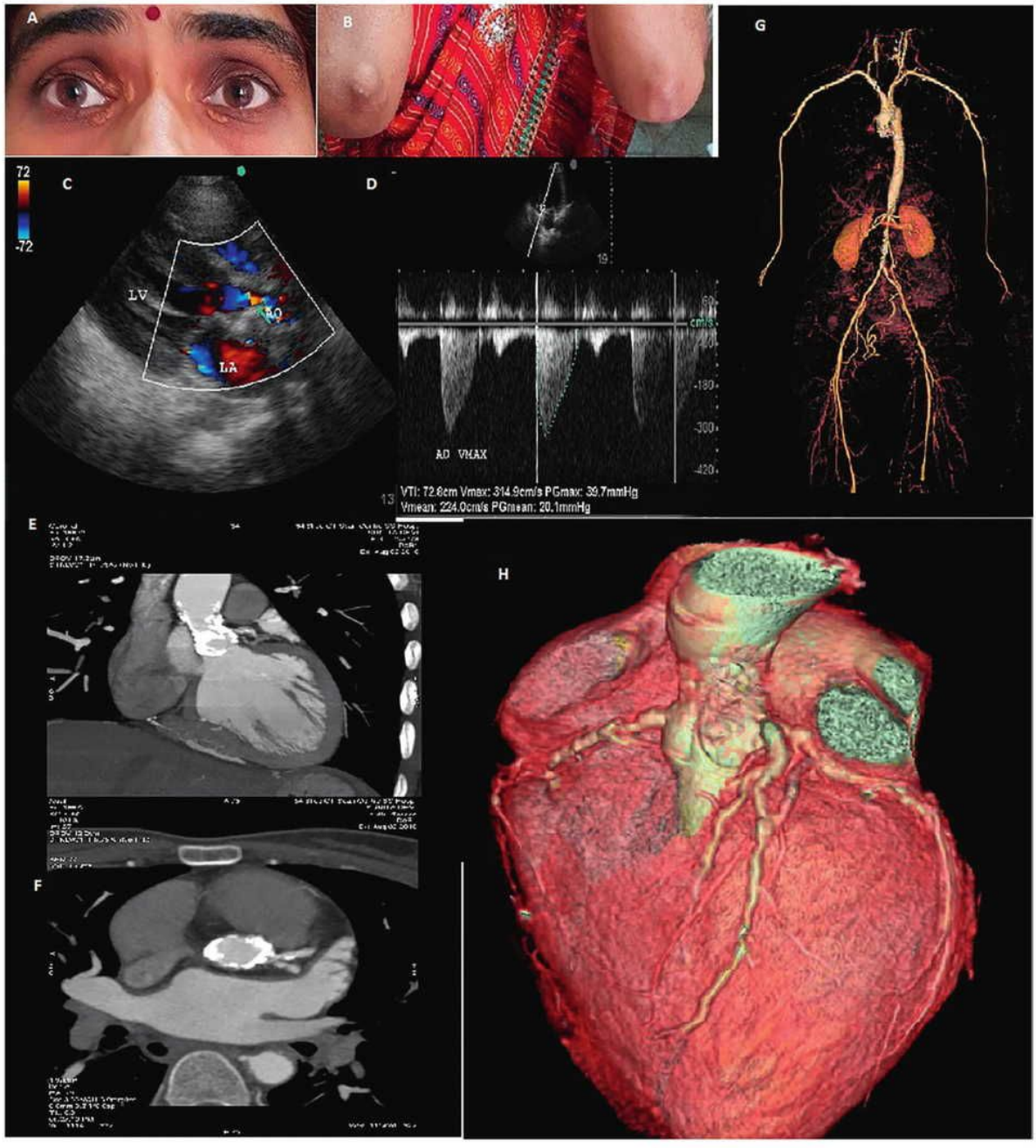

Fig. 1. A: Xanthelesma, B:Tuberous xanthomas over extensor aspects of elbow, C: Parasternal long axis view on colour doppler echocardiogram showing turbulence at the supravalvular level in the aorta, D: CW doppler shows a mean gradient of 20 mmHg, E,F: Severe calcification involving the aortic root and ascending aorta on CT, G: Contrast enhanced CT showing significant luminal narrowing in left common carotid, abdominal aorta, H: CT coronary angiography showing diffuse calcified triple vessel disease.

efficacious.[6] Addition of ezetimibe to statins has been shown to ehance their effectiveness. The effects of combined treatment of statins and ezetimibe have been reported to reduce LDL upto 20% in some studies.[7]

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab have been approved by the FDA in 2015. They are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL. Recent trials of PCSK9 inhibitors has demonstrated that PCSK9 inhibitors and statins reduce the risk of cardiovascular events proportional to the absolute reduction in LDLc and the total duration of therapy.[8] The NLA (National lipid asscociation) expert panel 2017 recommendations on treatment ofPCSK9 inhibitors recommends that PCSK9 inhibitor therapy may be considered to further decrease LDLc in patients age 18–39 years with pretreatment LDLc $\geq$ 190 mg/dl and the presence of either uncontrolled ASCVD risk factors, key additional risk markers, or genetic confirmation of FH, and ontreatment LDLc $\geq$ 100 mg/dl or non HDLc $\geq$ 130 mg/dl on maximally tolerated statin $\pm$ ezetimibe.[9]

Lipid apheresis is an accepted method for treating patients with heterozygous familial hypercholesterolemia who are unresponsive to pharmacologic therapy or for those with the homozygous disease type. It is advised to combine apheresis with maximum tolerated doses of statins plus ezetimibe. Liver transplantation and

portacaval anastomosis may be considered in patients not responsive to routine pharmacologic treatments.

Hypercholesterolemia can affect heart and vascular system, especially the coronary arteries, heart valves, and carotid arteries. In the homozygous type, the symptoms present in early years of life. Coronary angiography should be done to demonstrate the extent of coronary involvement, which can be at an advanced stage. Coronary artery bypass graft (CABG) could be the preferred treatment option because of diffuse disease and frequent left main involvement. Management of aortic involvement can be pharmacologic or surgical, depending on the severity of the disease. Favorable effects of using statins to slow the progression of AS have been reported.[10] In case of severe AS, aortic valve replacement, which is accompanied by favorable outcome, is recommended in such patients.[11]

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