

Familial Dysbetalipoproteinemia: A Potentially Fatal Disorder

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ABSTRACT

Familial dysbetalipoproteinemia is an inherited disorder in which both cholesterol and triglycerides are elevated in the plasma of the blood, which pre-disposes people to coronary artery disease and peripheral vascular disease. We report two young boys with multiple cutaneous xanthomas and grossly abnormal serum cholesterol and triglycerides. Two of the family members had died of cardiovascular accidents in young age and rest of the family members had deranged lipid profile. Patients were managed with lipid lowering drugs and fat restriction diet. All family members were counseled and advised regular exercise and follow-up.

Key words: *Dysbetalipoproteinemia. Familial dysbetalipoproteinemia. Broad beta disease. Defective apolipoprotein E. Type III hyperlipoproteinemia. Remnant particle removal disease.*

INTRODUCTION

Familial Dysbetalipoproteinemia (FDL) also known as hyperlipoproteinemia type-III, or broad beta disease, is a rare genetic disorder characterized by improper metabolism of certain lipids, specifically plasma cholesterol, triglyceride rich chylomicron and Very Low Density Lipoproteins (VLDL) remnants. This results in the abnormal accumulation of lipids in the body. Affected individuals may develop multiple yellowish, lipid-filled papules or plaques on the skin (xanthomas) and premature atherosclerosis resulting in coronary heart disease or peripheral vascular disease.¹ Hyperlipidemia is due to an increase in cholesterol-rich VLDL of abnormal electrophoretic mobility. Apolipoprotein E is a major protein constituent of VLDL and appears to be important for the hepatic uptake of triglyceride-rich lipoproteins. Most cases are inherited as autosomal recessive trait and can be traced to defects in the gene for apolipoprotein E.¹⁻³ The disease is usually not evident by elevated blood levels or symptoms until the age of 20 years or later. Xanthomas are the characteristic skin lesions that may appear on the palm of the hand, sole of the foot, or on tendons of knees and

elbows, and on the eyelids.^{4,5} Atherosclerosis develops in the coronary arteries, internal carotid arteries that supply blood to the brain, and the abdominal aorta and its branches. Affected individuals may develop angina, transient ischemic attacks or intermittent claudication of the legs. Hypothyroidism, obesity, diabetes, family history of familial dysbetalipoproteinemia or coronary artery disease are the additional risk factors.

The goal of treatment is to control underlying conditions, restriction of excess calories and the reduction of saturated fats and cholesterol. If high cholesterol and triglyceride levels still persist despite these measures, cholesterol lowering agents should be started. Nicotinic acid (niacin), clofibrate, statins or gemfibrozil are known to have effectively reduced cholesterol and triglycerides in people affected with dysbetalipoproteinemia.^{1,6,7}

CASE REPORTS

Case 1: A 13-year-old boy presented with history of progressive, non-itchy, yellowish, irregular plaques on elbows, knees, shoulders and buttocks since infancy. During the last 2 years, he had developed bilateral firm swellings on posterior aspect of his ankles along Achilles' tendons which resulted in difficulty in walking for about one month. Lesions were initially small and discrete but gradually coalesced into raised geographically shaped yellowish plaques (Figure 1). Extensor tendons of hands were thickened and beaded at places. His father had acute myocardial infarction at the age of 42 years. His mother and all other siblings were apparently normal. On laboratory examination, he was found to have hemoglobin of 11.7 g/dl, ESR at 40 mm at the end of 1st hour, serum cholesterol of 25.5 mmol/L, serum triglyceride of 10.3 mmol/L, serum HDL of 0.859 mmol/L and serum LDL of 13.4 mmol/L all being higher than normal range. Liver function tests,

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Figure 1: Yellowish-orange coloured papules and plaques of variable sizes over elbows and buttocks.

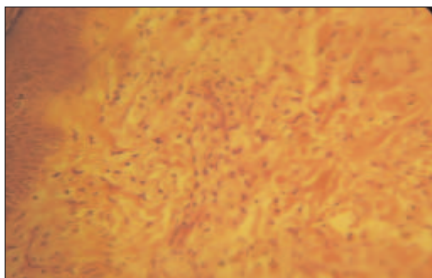


Figure 2: Histopathology showing infiltrate of foamy histiocytes dispersed in collagen fibers.



Figure 3: Discrete, rounded skin coloured swellings on dorsum of inter-phalangeal and carpo-metacarpal joints of hands (tendon xanthomas).

renal function tests and blood sugar levels were within normal limits. Echocardiography and X-ray chest were normal but ECG showed inverted T-waves in V1-V3 leads. Skin biopsy of one of the skin lesions from elbow showed flattened epidermis and an infiltrate of foamy histiocytes dispersed in collagen fibers (Figure 2). He was advised restriction of fat in diet, regular moderate exercise and was started oral atorvastatin 40 mg and gemfibrozil 600 mg once daily. Regular monthly follow-up was done and after 6 months, serum cholesterol and triglycerides levels had reduced markedly but there was no change in skin lesions.

He had two sisters and two brothers. One of his brothers (who had similar skin lesions) died of acute cardiac event at the age of 17 years. Other brother aged 11 years old had increased levels of serum cholesterol and triglycerides (8.2 and 6.2 mmol/L respectively) but did not have any cutaneous or systemic features of the disease. Both sisters (aged 15 and 26 years) also had increased serum levels of cholesterol and triglycerides but were also free of all symptoms and signs of dysbetalipoproteinemia. Their mother had goiter but no other abnormality. Although the surviving siblings did not have features of disease but they were counseled and educated about the disorder and started simvastatin 20 mg daily. They were also advised low-fat diet, regular exercise and follow-up in medical outdoor after every 6 months.

Case 2: A 22-year-old male (first cousin of case-1) also reported with history of progressive, non-itchy, yellowish, irregular plaques on elbows, shoulders and buttocks since infancy. In addition, he also had firm, discrete, rounded and skin coloured swellings of variable sizes on dorsum of interphalangeal and carpo-metacarpal joints of hands (Figure 3), on buttock, pretibial tuberosity and medial malleolar regions along with remarkable diffuse thickening of both Achilles tendons. Palms and soles were spared. Arcus juvenalis was noted in his both eyes. Blood complete picture, liver function tests, renal function tests and blood sugar levels were within normal limits. Serum cholesterol was 15.5 mmol/L, serum triglyceride was 10.3 mmol/L, serum HDL was 0.807 mmol/L and serum LDL was 11.1 mmol/L. X-ray chest was normal. ECG showed inverted T-wave in V1-V3

leads and echocardiography revealed aortic stenosis. Histopathology of one of the skin lesions was suggestive of xanthoma. In addition to fat restricted diet plan and moderate physical exercise, he was also started atorvastatin 40 mg and gemfibrozil 600 mg once daily. Regular monthly follow-up was done and after 6 months, serum cholesterol and triglycerides levels had reduced markedly but skin lesions persisted in this patient as well.

DISCUSSION

Familial dysbetalipoproteinemia is a highly atherogenic genetic disorder of lipoprotein metabolism that has a high incidence of cardiovascular complications, severe hypertriglyceridaemia and potential pancreatitis.^{1,8} FDL has been reported to be associated uniquely with an apolipoprotein E phenotype (E2/2) that occurs in approximately 1% of all persons.² Although receptor binding-defective forms of apolipoprotein (apo) E are the common denominator in this disorder, a number of apparent paradoxes concerning its pathogenesis still exist. An impact of other genes or hormones has been demonstrated in converting the hypolipidemia to hyperlipidemia.³ Men are considered more susceptible than women to FDL probably due to protective effect of estrogen on both LDL receptor expression and lipolytic processing, explaining the resistance of women to this disorder until after menopause.^{1,3}

These patients were young males, diagnosed on the basis of strong family history, characteristic skin lesions, very high serum levels of cholesterol and triglycerides and suggestive skin histology. They also had features of accelerated and premature atherosclerosis, exertional dyspnoea and ischemic changes in ECG. The family history and presence of cardiovascular symptoms was alarming and needed continuous and strict management plan to protect them or at least delay any future life-threatening cardiac event.

Siblings of the first case although had raised serum cholesterol levels, they did not have any cutaneous or systemic evidence of the disease. Probably sisters were protected due to some beneficial estrogenic effect and the younger brother possibly had disease manifestations later in his life. Considering the potential risks, all were advised to have fat restriction in their diet and regular monitoring of their serum lipids.

The present cases were reported at quite an early age as compared to the cases described in literature.¹ Total cholesterol and triglycerides levels were also found higher when compared with mean levels seen in a large retrospective study.¹ Palmar crease xanthomas and peripheral vascular disease was not seen in both cases, was found in 20% cases of the study by Bloom *et al.* In local literature, a family of hypercholesterolemia has been reported with multiple cardiovascular and skin manifestations.⁹ No cases of familial dysbetalipoproteinemia could be found in local literature and the present cases probably represent first reported cases from Pakistan. Considering fatal complications associated with familial dysbetalipoproteinemia, screening for family members becomes necessary as it may lead to early detection. Early treatment and avoiding other risk factors for vascular disease, such as smoking, are crucial to prevent early heart attacks, strokes and blocked blood vessels.

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