LETTER TO EDITOR (VIEWER'S CHOICE)

FAMILIAL HYPERCHOLESTEROLEMIA IN SIBLINGS WITH DIABETES MELLITUS

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Key words:

Familial hypercholesterolemia, children. Two siblings, an 8 years old girl and 5 years old boy, both of them diagnosed to have diabetes mellitus (DM) since 4 years of age were referred to our diabetic clinic for glycemic control. Family history suggested the paternal grandmother to be a diabetic at 60 years of age. There was no history of obesity or premature deaths in the family. On examination the girl child weighed 19 kg, her body mass index (BMI) was 17.92. Her blood pressure was 90/62mm of Hg. She had bilateral partial arcus juvenalis and multiple xanthomas over the back of the elbows and over the gluteal region. Papular, raised discrete yellowish lesions were seen typical of tuberous xanthomas (Fig 1). Her systemic examination was normal. The younger sib weighed 13 kg and his BMI was 16.05 and blood pressure was 80/60mm of Hg. He had bilateral partial arcus juvenalis and his systemic examination was normal. Echocardiogram revealed a normal study in both children. Laboratory parameters are tabulated (Table 1). Their mother showed high cholesterol 283mg/dl, low-density lipoprotein (LDL) Cholesterol 233 mg/dl, her blood sugar was 70mg/dl. She had no corneal arcus or xanthomas. Father was not available for the investigations. Both the children had their insulin dosage modified for glycemic control, were advised dietary restriction of fat, permissible exercise, statins and periodic review.

Figure 1: Xanthomas over elbow

Parameters	8 years old girl	5 years old boy
Blood Glucose (mg/dl)	335	353
Total Cholesterol (mg/dl) (Normal < 170 mg/dl)	697	686
Low-density lipoprotein (LDL) Cholesterol (mg/dl) (Normal < 110 mg/dl)	637	634
Triglycerides (mg/dl)	178	144
High-density lipoprotein (HDL) Cholesterol (mg/dl)	24	23
VLDL Cholesterol (mg/dl)	36	29
Glycosylated Hemoglobin (%) (Normal < 6%)	11.6	9.7
C-Peptide (pmol)	<0.3 (poor pancreatic reserve)	<0.3
GAD antibodies (IU/ml) (Normal <10 IU/ml)	10.1	12.5
IA2antibodies (IU/ml) (Normal <10 IU/ml)	<3	<3
Thyroid profile / Antibodies	Normal	Normal

Cardiovascular disease (CVD) is a leading cause of death worldwide. The strongest risk factors include a high concentration of LDL cholesterol, a low concentration of HDL, elevated blood pressure, diabetes mellitus, smoking, and obesity. (1,2) Familial hypercholesterolemia (FH) is the most common primary hyperlipidemia. FH is a monogenic autosomal dominant disorder due to a defect in LDL receptor leading on to increased LDL cholesterol concentration. The prevalence of heterozygote FH is 1 in 500. Since they have one normal allele they can remove about half of the plasma LDL and their LDL levels are increased to about twice normal. The increased cholesterol leads to symptoms by third-sixth decade. Homozygous FH is rare and occurs in 1 in a million, with both mutant alleles, they are unable to clear LDL from plasma and their LDL levels are more than 5-6 times normal. Children with homozygous FH may have symptoms of ischemic heart disease, cerebrovascular disease and articular symptoms. The total cholesterol and LDL cholesterol are more than 600 mg/dl. In the absence of interventions to decrease the cholesterol, their survival beyond adulthood is unlikely. Early recognition is crucial in preventing premature coronary artery disease.

Xanthomas provide a cutaneous marker of the silent underlying pathology. Cutaneous xanthomas at birth

or early childhood planar xanthomas are diagnostic of homozygous FH. Corneal arcus is highly unusual in children and its presence warrants work up for homozygous FH. Genetic testing and LDL receptor assay is confirmatory (3). The clinical presentation suggests a homozygous FH in these siblings.

Total cholesterol < 170mg/dl and LDL cholesterol < 110mg/dl are acceptable (1). Dietary history, tobacco use and physical activity should be noted in older children. Anthropometry, pubertal changes, presence of acanthosis should be noted. Management depends on the LDL levels as shown below:-

LDL < 110mg/dl	LDL 110 - 129 mg/dl	LDL > 130mg/dl
Repeat after 5years. Life style modification	AHA step 1 diet. Life style modification. Repeat LDL after 1 year	AHA step 1 diet. Life style modification. Repeat LDL after 3 months. If<130mg/dl continue the same If>130mg/dl add AHA step 2 diet . Repeat after 3 months If >130 mg/dl add drugs

Life style modifications include 60 minutes of vigorous play or aerobic activity per day. Sedentary play, watching video games and television should be discouraged as also alcohol and tobacco use, identify and treat eating disorders. Step1 diet is <10% calories from saturated fat, 30% from fat, <300mg from cholesterol. Step 2 is 7% from saturated fat, cholesterol <200mg/day (4). Statins have been found to be useful and safe in children 8 years onwards (5). Average starting doses will be rosuvastatin 5 mg, atorvastatin 10 mg and simvastatin 20 mg/day, with a close watch on side effects. Ezetimibe has been approved for use in children more than 10 years as an add on drug (6). The response to drug therapy may not be good as in heterozygous hypercholesterolemia. Pharmacologic management should be considered in patients aged 8 years or older with an LDL cholesterol level of 190 mg/dL or more, 160 mg/dL or more with a family history of early cardiovascular disease or additional risk factors or 130 mg/dL or more in a patient with diabetes mellitus (2). Pharmacologic intervention in children younger than 8 years can only be implemented if they have the dramatic elevation of LDL concentration (>500mg/dL). In children aged 10 years and older with homozygous FH, biweekly apheresis with plasma exchange for removal of LDL particles is helpful. Liver transplantation has been successful to reduce the LDL levels but complications related to immuno suppression are common. Early initiation of therapy in children with FH might be beneficial in the prevention of atherosclerosis in adolescence (5). Moreover if the first degree relatives of a patient are screened other gene carriers can be identified and treated to prevent the complications later.

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