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WHAT'S YOUR DIAGNOSIS?

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Figure 1: hard tubero-nodular swellings of the feet.

Figure 2: Nodular swellings of PIP and MCP joints.

History

A 19-year-old, single Nepali female who was a teetotaler, presented with multiple swellings in both hands and feet which had been present since the age of six, and which were gradually increasing in size. For the previous two years, she had also been complaining of central chest pain and breathlessness on and off, especially on exertion. The present admission was due to a huge swelling, excruciating pain in both knees, and fever of two days' duration. There was no early morning stiffness. Family history revealed that the father died of heart attack before the age of 50, two sisters and two brothers died in childhood, and one brother who had similar nodular swellings of the hands and feet, died suddenly at the age of 25. The remaining brother was asymptomatic at the age of 23.

On clinical examination, there was no anemia, edema, or lymphadenopathy. The pulse was 74/min and regular, and BP was 110/80 mm Hg. Chest, abdominal and neurological examinations were unremarkable. CVS examination revealed grade 1 ejection systolic murmur at the aortic area.

Local examination of the swellings revealed many hard, tubero-nodular, non-tender, immobile swellings on the lateral border of the feet (Figure 1). There were multiple hard nodular swellings at the proximal interphalangeal (PIP) and metacarpophalngeal (MCP) joints (Figure 2), as well as the wrists and triceps tendons. Arcus juvenilis was present bilaterally. Tuberous swellings were present on buttocks. Fundoscopy was normal. CBC, RA factor, urine R/E, LFT, blood urea, serum creatinin, FBS, T4, T3 and TSH were all within normal limits. ESR was 80 mm in the first hour.

1. What would be the most appropriate investigation?

2. What is the diagnosis?

ANSWER TO WHAT'S YOUR DIAGNOSIS?

Figure 1 Hard tubero-nodular swellings of the feet.

Investigations: The most appropriate investigation would be fasting lipid profile of the patient, x-ray of the hands and feet, ECG, chest x-ray, echocardiography, tread mill test and biopsy of the nodular swelling (Figures 1 & 2).

Diagnosis: Homozygous familial hypercholesterolemia (FHC).

Discussion: Most cases of homozygous FHC occur in societies where consanguineous marriages are prevalent. In the Arab world, consanguineous marriage is common, but among Hindus in Nepal, it is almost unknown. The parents of our case were not known to each other before marriage.

The chance of marriage between unrelated heterozygotes in Britain or America is 1 in 500 and the chance of each of their children developing homozygous FHC is 1 in 4. In reality, abortion, stillbirth, infant deaths are very common, and if they survive, the chance of becoming a grown-up child with homozygous FHC will be 1 in 1,000,000. Unfortunately, the living brother and mother of our patient were not available for screening for cholesterol. It can be strongly assumed that the brother was a normal healthy subject, but the mother may have been a heterozygote with less penetrance to contribute the abnormal allele to the proband case.

Clinically, such a child develops cutaneous xanthoma in childhood before the age of 10 years. They may develop coronary artery disease and valvular stenotic lesions in the first few years of life, especially during adolescence. Typically, orange-yellow subcutaneous planar xanthomata

Figure 2: Nodular swellings of PIP and MCP joints.

occur on the buttocks, ante-cubital fossa of hands and the webs of fingers. Tuberous subcutaneous xanthoma on knees, knuckles, and wrist is also a diagnostic feature. Myocardial infarction and angina frequently occur in childhood, sometimes even in infancy.[4] Atheromatous

plaque at the aortic root is invariably present at puberty. They produce significant aortic stenosis, which contributes to sudden death.[6] Death invariably occurs before the age of 30, if plasmapheresis drug therapy and similar techniques are not sought to remove LDL cholesterol. Polyarthritis affecting the ankles, knees, wrists and proximal interphalangeal joints is frequently seen in homozygous FHC. The present case had bilateral knee joint swelling and all MCPs and PIPs of fingers involved.

Our patient is still under treatment with lovastain and nitrates. Probucol (an antioxidant) which is not available in Nepal, can reduce the cholesterol by a non-LDL receptor mediated pathways. This drug can also cause some regression of xanthomas. We do not have facilities such as plasmapheresis, which is done in other specialized centers. Our patient has not responded much to drugs and diet. In Western countries, heparin extracorporeal LDL precipitation (HELP) can reduce the LDL load. Portacaval shunt (decreases hepatic cholesterol biosynthesis) or orthotopic liver transplantation (donation of LDL receptors to the patients) are in the experimental stage.[3] The late development of coronary arterial disease in the present case may be due to the protective effect of female hormones in spite of altered lipid metabolism. The sudden death of four siblings in early childhood was assumed to be due to stenotic coronary or aortic valvular lesion. Postmortem would have shed light on the cause of sudden death of her father and brother, however, facilities were not available in Nepal at the time.

The family pedigree of the present case depicts a metabolic disorder of the autosomal dominant type. One parent was affected and both sexes of the offsprings were also affected. The present case must have inherited two mutant alleles from the two parents. She might have had some LDL receptor activity, which prevented development of early myocardial infarction. This can be proved only by fibroblast culture and by measuring the LDL receptor activity in vitro.

Most probably, this was not a case of a psuedo-homozygous type II FCH because one of her parents died of heart attack and the lipid-lowering drugs had no effect on her cholesterol at all.

Mechanism of Homozygous FHC

Normally, a healthy subject has LDL cholesterol half-life of 3 days. Heterozygote FHC has half-life of 5 days and homozygote FHC has 7 days. Decreased clearance of LDL cholesterol (defect in the LDL receptors leading to inadequate hepatic uptake of LDL cholesterol) leads to increase in circulating LDL cholesterol.[5]

The gene-coding LDL receptor is located on the short arm of chromosome 19. Heterozygotes express only about 50% of LDL receptor activity whereas homozygotes express only up to 25% of normal LDL receptor activity.[2]

Both parents contribute abnormal allelic doses of FHC gene in a homozygote while only one parent contributes one abnormal allelic dose of FHC gene in heterozygote. There are either defective or dysfunctional LDL receptors responsible for FHC and this defect is brought about by mutational changes, which may be more than 200. Sophisticated DNA testing in fibroblastic culture, can detect these mutational changes, but such facilities are not available in this country.

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