**Case report**

Treatment of the arthropathy of familial hypercholesterolaemia

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**Summary** A 29-year-old woman suffering from the arthropathy of familial hypercholesterolaemia was treated with a fat-modified low-cholesterol diet and colestipol. Symptomatic improvement occurred in association with a moderate reduction in the plasma cholesterol concentration. The pathogenesis of the musculoskeletal features of this disease is reviewed, and the implications of this patient's therapeutic response are explored.

Familial hypercholesterolaemia (Fredrickson's type IIa hyperlipidaemia) is characterised by high concentrations of low-density lipoprotein (LDL) cholesterol, corneal arcus, tendon xanthomata, and premature atherosclerosis. Involvement of the joints was first described by Khachadurian, who recognised that migratory polyarthritis was a manifestation of the hyperlipidaemia and not due to coincidental rheumatic fever. Although he reported this arthropathy in homozygotes, Rooney and others have recently described polyarthritis in 7 of 44 patients with heterozygous type IIa hyperlipidaemia. The musculoskeletal manifestations of the disease are important because they may be the presenting features, and their correct recognition can lead to an early diagnosis and appropriate treatment. Conventional treatment of the disorder includes a fat-modified diet and bile acid sequestrants. Although these measures have been shown to lead to a reduction in LDL cholesterol concentrations, the outcome of the arthropathy in patients so treated has not been previously reported.

In this communication the clinical features and laboratory findings in a patient with the arthropathy of familial hypercholesterolaemia are described. The progress of the arthropathy following the introduction of specific therapy is reported, and the pathogenetic implications of the therapeutic response are discussed.

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**Case report**

A 29-year-old woman was admitted to Royal Perth Rehabilitation Hospital in January 1980 for investigation of a recurring polyarthritis. At the age of 3 years she had developed tender swellings round the tendo Achillis of both feet which were attributed to bursitis. Attacks of large-joint pain began soon after, and continued to occur 2 to 3 times each year. The symptoms usually began in a knee, then involved the opposite joint and advanced to the ankles over a period of days, the articular involvement being additive and usually confined to the lower limbs. The intensity and duration of the symptoms was variable, but on many occasions she was incapacitated for up to 6 weeks.

A family history of arthritis was elicited in a maternal uncle with hypercholesterolaemia. Her father was well and her mother had committed suicide. She had suffered from a depressive illness. Neither parent was known to be subject to arthritis or to have a disorder of lipid metabolism. There was no family history of premature atheroma. The patient had no siblings.

Physical examination disclosed an irritable, emotionally labile woman who lay motionless in the fetal position and resisted movement of her joints. Incomplete corneal arcus and Achilles tendon xanthomata were noted (Figs. 1 and 2). The knees, ankles, and feet were tender but not swollen or hot. No effusions were detected. The remainder of the examination, including the cardiovascular system in particular, was normal.

Investigations revealed a raised erythrocyte sedimentation rate (ESR), 64 mm/h, a normal
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Fig. 1 *Incomplete corneal arcus.*

Fig. 2 *Achilles tendon xanthomata.*
haemoglobin and white cell count, and negative tests for rheumatoid factor and antinuclear antibodies.

Radiographs of the knees were normal. Serial streptozyme and anti-DNA-ase B titres were constant. The low-density lipoprotein cholesterol concentration in a specimen of fasting blood was 12.3 mmol/l and the triglyceride concentration in the same specimen was 1.2 mmol/l.

A diagnosis of familial hypercholesterolaemia was made. In the absence of any evidence of vascular disease, and in view of her family history, homozygosity was considered improbable.

The polyarthritis gradually resolved over a period of 7 days. Treatment with a fat-modified low-cholesterol diet was initiated, and colesterol was subsequently added. The plasma cholesterol concentration fell slowly and then stabilised as shown in Fig. 3. There has not been a recurrence of the disabling polyarthritis which precipitated her admission to hospital, though she has had 2 episodes of transient lower limb pain (as shown in Fig. 3), both of which differed considerably from the polyarthritis to which she was subject.

She has experienced a number of side effects directly attributable to colesterol. These include nausea, flatulence, mild intermittent abdominal pain, and periodic looseness of stools.

Discussion

The nature of the arthritis which occurs in familial hypercholesterolaemia is a matter for conjecture. Uncertainty exists about not only the cause of the symptoms but also their precise location. Both intra-articular and periarticular disease have been suggested. Rooney et al. have argued that the symptoms are due to a periartritis and advanced scintigraphic evidence to support this concept. Glueck and others favour a synovitis on the basis of the leukocytosis occasionally found in the synovial fluid.

Although joint effusions occur occasionally in this disorder, they are exceptional, suggesting that the pathology may well be periarticular. Some of the manifestations of the arthritis are very similar to those found in the periartitis which occurs in uraemic patients receiving dialysis. In both disorders it is the large joints which are mainly affected, the onset is abrupt, and the course is self-limiting. Moreover the scintigraphic evidence for extrasynovial inflammation strengthens the case for periarticular pathology.

The possibility of a cholesterol-crystal-induced arthritis has also attracted attention. Most investigators have interpreted the absence of significant quantities of crystals in the synovial fluid as evidence against this concept. It is of interest, however, that Delbarre and others have recently found microcrystalline cholesterol in synovial membrane obtained from a patient with familial hypercholesterolaemia from whom a biopsy specimen was taken during a flare-up of her arthritis. Although the significance of this finding cannot be determined in the absence of information about the presence of such microcrystalline deposits in asymptomatic persons with this disease who are not subject to arthritis, its relevance to the pathogenesis of the arthropathy merits further consideration.

Experimental evidence exists for the possible role of cholesterol crystals in soft-tissue and joint inflammation. Denko and Petricevic have shown that cholesterol crystals injected into the foot pads of rats produce local inflammation comparable to that
induced by urate crystals.\textsuperscript{12} In addition Bland \textit{et al.} have demonstrated that cholesterol crystals injected into the knee joints of rabbits cause a transient synovitis.\textsuperscript{12}

The relationship between the plasma cholesterol concentration and the arthropathy of familial hypercholesterolaemia has not been determined. Khachadurian could not demonstrate a temporal relationship between high cholesterol concentrations in the plasma and the onset of episodes of polyarthritis.\textsuperscript{3} In the patient reported here, however, a typical attack of polyarthritis did coincide with a slight but definite rise in the plasma cholesterol concentration (as shown in Fig. 3). The cholesterol concentration for September 1979 was determined retrospectively from stored serum. The predilection of the arthropathy for homozygotes suggests that the relative risk for the arthritis might be proportional to the cholesterol concentration, in the same way as the risk of gouty arthritis is related to the serum uric acid level. If this were true, then a reduction in the plasma cholesterol concentration could be expected to have a favourable effect on the arthritis. The therapeutic response in the patient reported here is consistent with this hypothesis in so far as the attacks of incapacitating arthritis abated when the plasma cholesterol concentration was reduced.

Further advances in our understanding of the pathogenesis of type IIa hyperlipidaemia may lead to improved treatment and prevention of the musculoskeletal and other manifestations of this disease. In the meantime conventional treatment must suffice. The response of the patient described in this report tends to suggest that standard therapy for familial hypercholesterolaemia may not only improve the cardiovascular prognosis, but also benefit those in whom rheumatic symptoms are prominent.

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