Articular manifestations of familial hypercholesterolaemia

GILLES MATHON, CLAUDE GAGNÉ, DANIEL BRUN, PAUL-J LUPIEN, AND SITAL MOORJANI

From the Service of Rheumatology and Lipid Research Center, Department of Medicine, Le Centre Hospitalier de l'Université Laval, 2705 Boulevard Laurier, Québec, Canada G1V 4G2

SUMMARY Familial hypercholesterolaemia is characterised by a decreased removal of low density lipoproteins and premature coronary artery disease. Tendinous xanthomata are a hallmark of the disease. The affected joints may also be the sites of inflammation and pain. Arthropathy has been associated mainly with the homozygous form of familial hypercholesterolaemia, but it is also known to occur in the heterozygous form. We report on the articular manifestations in 73 patients with heterozygous familial hypercholesterolaemia. About 40% of these patients had at least one episode of articular symptoms. The observed articular manifestations may be classified into four types: Achilles pain (18%), Achilles tendinitis (11%), oligoarticular arthritis (7%), polyarticular or rheumatic fever-like arthritis (4%). It is concluded that in heterozygous familial hypercholesterolaemia articular manifestations are frequent, diverse, and may be the first symptom of this metabolic disorder.

Key words: arthritis, tendinitis, tenosynovitis, Achilles tendons.

Familial hypercholesterolaemia is a relatively common autosomal dominant disorder, characterised by increased total and low density lipoprotein (LDL) plasma cholesterol levels, premature coronary artery disease, and tendinous xanthomata. The cause of the rise of plasma cholesterol levels is a decreased removal of LDL due to a defect in their specific peripheral receptors.¹

There are two clinical forms of familial hypercholesterolaemia. In the rare homozygous form LDL cholesterol levels are above 500 mg% and xanthomata appear during infancy and childhood; coronary artery disease occurs during the second decade of life. In the heterozygous form LDL cholesterol levels are around 300 mg/dl (7.8 mmol/l), tendinous xanthomata appear in the second and third decades of life, and coronary artery disease is rarely seen before the age of 30.

It is well known that tendinous xanthoma, a diagnostic sign of familial hypercholesterolaemia,² may frequently be the site of pain and inflammation. Some authors have described tendinitis, tenosynovitis, arthralgia, and migratory polyarthritis in both

homozygous and heterozygous familial hypercholesterolaemic patients.³⁻⁷ In order to characterise further the different articular manifestations of familial hypercholesterolaemia we studied 73 patients with the heterozygous form of this genetic disorder.

Patients and methods

PATIENTS

The patients were diagnosed as having heterozygous familial hypercholesterolaemia according to the following criteria: the presence of hypercholesterolaemia (age adjusted) but below 500 mg/dl (13 mmol/l) for LDL cholesterol, and the presence of tendinous xanthomata. In the absence of tendinous xanthoma in a proband hypercholesterolaemia and tendinous xanthomata were considered as essential findings in at least one first-degree relative. Secondary forms were excluded by the appropriate diagnostic procedures.

Seventy-three consecutive patients (45 female, 28 male) seen at the Lipid Clinic of Laval University Hospital Center were interviewed and examined. The questionnaire was standardised and included

past rheumatological history and present symptoms. A complete articular examination was performed by one of us (GM).

LIPIDS AND LIPOPROTEINS

Total cholesterol and triglyceride levels were determined simultaneously after extraction of plasma with isopropanol and treatment with zeolite mixture on Auto Analyser II (Technicon Instruments Inc., Tarrytown, New York). Very low density lipoproteins (VLDL) were isolated by ultracentrifugation at a density of 1.006 g/ml as described by Havel *et al.*⁸ High density lipoprotein cholesterol was measured in the bottom fraction (density greater than 1.006 g/ml) after precipitation of LDL with heparin (6%) and manganese chloride (0.092 mol/l final concentration) as described previously.⁹

LDL cholesterol was obtained by the difference in the concentration of cholesterol before and after precipitation of the plasma fraction of density greater than 1.006 g/ml. Total apoproteins A and B, and LDL apoprotein B were measured by rocket immunoelectrophoresis.¹⁰

Results

PATIENTS, LIPID AND LIPOPROTEIN LEVELS (Table 1)

The mean age of the 73 patients was 35.3 ± 16.8 years (mean $\pm$ SD) (range 5 to 68 years). 80% of the patients were 20 years or older.

Total cholesterol, LDL cholesterol, total apoprotein B, and LDL apoprotein B were increased respectively at 364.2 ± 66.9 mg/dl (9.43 ± 1.73 mmol/l), 307.5 ± 64.1 mg/dl (7.96 ± 1.66 mmol/l), 2.02 ± 0.54

Fig. 1 Articular manifestations in 73 patients with the heterozygous form of familial hypercholesterolaemia. (RF-like=rheumatic fever-like.)

g/l, and 1.83 ± 0.42 g/l. (These values are given as mean $\pm$ standard deviation of the mean.)

ARTICULAR SYMPTOMS (Fig. 1)

Twenty-nine patients (40%) had suffered from articular manifestations at some time. These manifestations were of four types: Achilles pain, Achilles tendinitis, oligoarthritides, and polyarthritides (rheumatic fever (RF) type). Seven of them reported more than one type of articular or periarticular symptoms, representing a total of 33 manifestations.

The most frequent manifestation was Achilles pain (18% of the patients) in which limping was the only sign and lasted only for a few hours. It recurred frequently.

Tendinitis of the Achilles tendons was frequent (observed in 11% of the subjects) and was characterised by a subacute onset, often associated with prodrome and always accompanied by inflammation. All patients had a severe limp, and they were frequently bedridden. The duration of each episode was short, averaging from two to three days, but the recurrences were frequent (two or three times a year). The Achilles tendons remained symptom free between attacks, though it was quite often inflamed at the time of examination. The mean age of onset was 17 years.

7% of the patients had a mono-oligoarticular arthritis, and the affected joints were the knees in six instances, the ankles in three, and the proximal interphalangeal joint in one patient. All patients described the arthritis as very acute and severe enough to necessitate bed rest. Each episode lasted a few days (mean duration 10 days), and the involved joint always returned to normal function.

Table 1 Patients, * lipids and lipoproteins

	n	Lipid and lipoprotein concentrations	
		(mg/dl)	(mmol/l)
Total cholesterol	73	364.2±66.9†	9.43±1.73†
VLDL cholesterol	65	22.5±28.9	0.58±0.75
LDL cholesterol	65	307.5±64.1	7.96±1.66
HDL cholesterol	73	38.8±10.1	1.00±0.26
Total triglycerides	73	137.0±74.3	1.55±0.84
Total apoprotein B	45	202.4±54.8	
LDL apoprotein B	45	183.1±42.0	
Total apoprotein A	45	176.8±36.1	

*Seventy-three patients (28 male, 45 female), age 35.3 ± 16.8 † years (range 5–68 years).

†Mean $\pm$ standard deviation.

Although the recurrences were frequent (up to 15 episodes in a period of 18 months in one patient), the affected joints remained asymptomatic between episodes. They were normal at the time we examined them. This type of arthritis usually made its appearance around the age of 20.

The polyarticular type (rheumatic fever type) was reported by 4% of the patients. It was characterised by systemic symptoms with fever, and the patient was always incapacitated. The polyarthritis was symmetrical, having an acute onset with severe clinical signs. In comparison with the mono-oligoarticular arthritis the illness lasted longer (mean duration about one month) but never recurred. One of the patients reported having been treated with penicillin and another having had a 'miraculous' recovery with corticosteroid treatment. After the illness the joints remained symptom free and were normal at the time of the examination. The mean age of occurrence for this type of arthritis was 18 years.

ARTICULAR SIGNS

58% of the subjects studied had bilateral Achilles xanthomata at the time of examination, and they were present unilaterally only in 2% of the patients. Patellar tendon and plantar xanthomata were both found in 8% of patients.

40% of the patients had xanthomata on the extensor tendons with a mean of 2.3 tendons infiltrated. Flexor tendon infiltrations were observed in 71% of patients, with a mean of 2.6 affected tendons per patient.

Discussion

Khachadurian,³ in 1968, was the first to report migratory polyarthritis in patients with homozygous familial hypercholesterolaemia. He described the characteristics of the articular disease and made the clinical distinction between this type of polyarthritis and rheumatic fever, which may have similar clinical and laboratory manifestations such as polyarthritis, heart murmurs, and an accelerated sedimentation rate. The same year Glueck and colleagues⁴ reported on the oligomonoarthritis and tendinitis affecting 14 patients with heterozygous familial hypercholesterolaemia. Later, Shapiro and colleagues⁶ described similar articular manifestations of heterozygous familial hypercholesterolaemia in children and adolescents. In 1978 Rooney and colleagues⁷ suggested that the syndrome had a periarticular pathogenesis.

In our retrospective study based on symptoms reported by 73 patients, mostly adults with the heterozygous form of familial hypercholester-

olaemia, we found that 40% had articular manifestations at some time during their life. The articular symptoms were of four types: mono-oligoarthritis, polyarthritis, Achilles tendinitis, and Achilles pain. The most frequent site of involvement was the Achilles tendon and the mono-oligoarticular or polyarticular arthritis were less common. In addition to tendinous xanthomata, which are characteristic of familial hypercholesterolaemia and are usually best observed on the Achilles, patellar, and extensor tendons of the fingers, we also found infiltrations of the flexor tendons.

The diagnosis of the hand flexor tenosynovitis was made according to the following criteria: crepitation, grinding, snapping, or locking on passive or active movement of the finger. They occurred in a non-specific fashion in 71% of the population studied.¹¹ However, they seem to be part of the disease, as they were associated with xanthomata of the extensor tendons in 83% of the cases, with no other medical manifestations apart from the familial hypercholesterolaemia to explain their high incidence in our population.

The articular manifestations in our heterozygous population of familial hypercholesterolaemia were frequent, diverse, recurrent, incapacitating, short lasting, and transitory. The joints remained symptom free between attacks, and they never progressed to articular damage or deformity as observed in the homozygous form. Although tendinous xanthomata were present in many of the patients at the time of examination, they may be absent when the symptoms occur. In fact, tendinous xanthomata rarely occur before the age of 20,¹² and Achilles tendon thickness shows a positive correlation with age in heterozygous familial hypercholesterolaemia.² Unless the existence of hypercholesterolaemia is known, the diagnosis may be difficult and articular symptoms and signs may lead to extensive investigation to identify the aetiology.

Articular symptoms may be the first clue to the diagnosis of familial hypercholesterolaemia, long before the appearance of xanthomata and ischaemic heart disease. The diagnosis of familial hypercholesterolaemia is important, as its treatment prevents the development of ischaemic heart disease¹³ and may also prevent the recurrence of the articular symptoms.¹⁴

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