EXTENDED REPORT

Familial hypercholesterolaemia commonly presents with Achilles tenosynovitis

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Background: Patients with heterozygous familial hypercholesterolaemia (HeFH) develop tendon xanthomata (TX), most commonly in their Achilles tendons. Even before tendons are chronically enlarged, tenosynovitis may occur and medical advice be sought. Untreated HeFH carries a high risk of premature coronary heart disease, which can be ameliorated by early diagnosis.

Objective: To determine the prevalence of episodes of Achilles tendon pain in HeFH before its diagnosis.

Methods: Patients with definite HeFH (Simon Broome criteria) attending a lipid clinic were identified. They completed a questionnaire asking about symptoms relating to their Achilles tendons. Unaffected spouses or cohabiting partners served as controls.

Results: 133 patients (47% men) and 87 controls (51% men) participated. TX had been recognised by the referring physicians in <5% of cases. However, 62 (46.6% (95% confidence interval (CI) 38.1 to 55.1)) patients had experienced one or more episodes of pain in one or both Achilles tendons lasting >3 days, whereas only 6 (6.9% (1.6 to 12.2)) controls had done so (difference $p < 0.001$; likelihood ratio 6.75). Typically, in the patients with HeFH the pain lasted 4 days (median). It was described as severe or very severe in 24/62 (38.7% (30.4 to 47.0)) patients with HeFH, but never more than moderate in controls. 35 (26.3% (18.8 to 33.8)) patients with HeFH had consulted a doctor about Achilles tendon pain, but in no case had this led to a diagnosis of HeFH. None of the controls had consulted a doctor.

Conclusions: Measurement of serum cholesterol in patients presenting with painful Achilles tendon could lead to early diagnosis of HeFH.

Heterozygous familial hypercholesterolaemia (HeFH) affects about one person in 500 in the United Kingdom. Untreated it is associated with a high mortality and morbidity from coronary heart disease (CHD).^{1,2} Recent evidence suggests that patients in whom the diagnosis is recognised and who receive intensive treatment, including advice about their lifestyle and statin treatment, can achieve a normal life expectancy.³ Detection of HeFH before the onset of clinically manifest CHD is thus exceptionally important. HeFH is due to a defect in the catabolism of low density lipoprotein (LDL), usually resulting from the inheritance of a mutant LDL receptor gene.¹ In the UK, several hundred different mutations can give rise to the syndrome,¹ with the commonest accounting for only a small proportion of cases.⁴ The usual means of diagnosis is thus by clinical phenotype. Generally in HeFH the serum cholesterol in adults exceeds 7.5 mmol/l and may occasionally be double this value. Most patients with HeFH, in addition, develop tendon xanthomata (TX) (fig 1). These become increasingly common from the third decade onwards.^{5,6} They do not occur in more common, generally less severe types of hypercholesterolaemia, such as polygenic hypercholesterolaemia and familial combined hyperlipidaemia, which occur later in life. The only other disorders in which TX are recognised are the extremely rare β -sitosterolaemia and cerebrotendinous xanthomatosis.⁷

Despite the obvious diagnostic importance of TX, few clinicians recognise them. Cholesterol testing in the UK in people aged less than 40 years is not often undertaken unless they have some particularly strong risk factor such as diabetes or hypertension. Yet HeFH, being a monogenic disorder, is not associated with other cardiovascular risk factors.⁸ We set out therefore to investigate how often

patients with HeFH had presented to their general practitioner as a consequence of TX, and in how many cases this had led to measurement of serum cholesterol and the diagnosis of HeFH. The Achilles (calcaneal) tendons are the most common site of xanthomata.^{6,8} Patients become aware of them as the consequence of pain and swelling due to local tenosynovitis. TX comprise cholesterol deposits together with inflammatory cells and a marked fibrous reaction (fig 2). Episodes of inflammation may occur for some while before the tendon is chronically enlarged.^{9–11}

METHODS

Patients aged >20 years attending the lipid clinic at the Manchester Royal Infirmary at least once in the preceding 12 months with a definite diagnosis of HeFH were asked to complete a questionnaire. This asked whether the patient had experienced pain in either of the Achilles tendons lasting >3 days, how severe it was, whether their doctor had been consulted, the frequency and duration of episodes, age of onset, physical trauma to the tendon, hospital treatment for the tendon, and presence of any arthritic condition (copies of the questionnaire available from PND). To serve as a control group, spouses or cohabiting partners of hypercholesterolaemic patients accompanying them to the clinic were also asked to complete a similar questionnaire. The clinical diagnosis of HeFH was based on the criteria of the Simon Broome Register: serum cholesterol >7.5 mmol/l and either TX in the patient or in a first or second degree relative.² The patients had presented at the clinic between 1987 and 2003 and the

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HeFH, heterozygous familial hypercholesterolaemia; LDL, low density lipoprotein; TX, tendon xanthomata

Figure 1 Achilles tendon xanthomata.

study was performed between 1 May and 31 July 2004. Investigators were blinded during data entry from questionnaires: serum cholesterol values and the identity of patients and controls were linked later.

The patients and controls gave their informed consent to participate in the study, which had the approval of the Central Manchester Research Ethics Committee.

Statistics

Results are presented as percentages (95% confidence intervals (CIs)). They were considered to be statistically significantly different, if 95% CIs did not overlap. The level of significance was then determined by χ^2 testing.

RESULTS

Of the 166 patients with HeFH approached, 133 (47% men) completed a questionnaire. The response rate was thus 80%. Eighty seven (51% men) spouses or cohabitantes were available to complete a questionnaire. The ages of the patients and controls were similar: 57 (42–64) (mean (interquartile range)) and 55 (44–64) years, respectively. On average, the patients had attended the clinic for 8 years. Serum cholesterol values obtained before lipid lowering treatment was started were available in 103 patients; the mean (SD) serum cholesterol concentration was 10.9 (2.4) mmol/l.

Figure 2 Microscopic section of an Achilles tendon xanthoma stained with haematoxylin and eosin, showing dense fibrous tissue surrounding spaces from which cholesterol (cholesterol clefts) has been dissolved out during fixation and paraffin embedding.

Figure 3 The age by which patients with heterozygous familial hypercholesterolaemia had experienced an episode of Achilles tendon pain lasting 3 days or more.

The diagnosis of definite HeFH had been made because, in addition to serum cholesterol >7.5 mmol/l, TX were present by inspection and palpation in 114 (86%) of the patients. In the 19 (14%) in whom TX were not detected at diagnosis, they were present in a first degree relative. TX had been recognised by the referring physician in $<5\%$ of patients. None the less 62 (46.6% (95% CI 38.1 to 55.1)) patients had experienced one or more episodes of pain in one or both Achilles tendons lasting longer than 3 days. Such a history was present in only six (6.9% (1.6 to 12.2)) controls, which was a significant difference ($p<0.001$).

The mean (SD) serum cholesterol at presentation to the clinic in patients with HeFH experiencing Achilles tendon pain (11.0 (2.4) mmol/l) was not significantly different from that in those who had not presented to the clinic (10.7 (2.5) mmol/l). Their age at presentation was also similar and in every case, when pain in an Achilles tendon had occurred, it had done so before presentation. The Achilles tendon pain in HeFH lasted a few days to several weeks (median 4 days). It was described as severe in 24/62 (38.7% (30.4 to 47.0)) patients with HeFH, but in none of the controls did it exceed moderate severity.

Episodes were similarly frequent in men and women with HeFH. Most male patients had experienced Achilles tendon pain by the age of 25 years whereas most women had not done so until the age of 30 (fig 3). Over 70% of both men and women with HeFH, who experienced Achilles tendon pain had done so before age 40. Most importantly, 35 (26.3% (18.8 to 33.8)) patients with HeFH overall had consulted a doctor about Achilles tendon pain, but in no case had this led to the measurement of serum cholesterol or to a diagnosis of HeFH. Most patients had been treated with non-steroidal anti-inflammatory drugs. A small number had been referred for an orthopaedic opinion, which had resulted in operative intervention in three. None of the controls had consulted a doctor about Achilles tendon pain.

DISCUSSION

More than a quarter of the patients with a definite diagnosis of HeFH had consulted their general practitioner about Achilles tendon pain and this had not led to the measurement of serum cholesterol and thus diagnosis of HeFH. It

Figure 4 Computer tomography of (A) normal Achilles tendons (B) Achilles tendon xanthomata.

seems likely that many of these patients would have had their Achilles tendons examined and that either they were not obviously xanthomatous or TX were not recognised by the examining physician. Certainly by the time of presentation to the clinic, four fifths had definite Achilles TX.

We have previously drawn attention to the fact that many patients with HeFH do not present to the lipid clinic until clinical CHD has already occurred.⁸ The detection of HeFH by screening the relatives of patients with HeFH in whom the diagnosis has been confirmed in a lipid clinic, however, frequently yields a higher proportion who have yet to develop CHD.⁸ This seems important given the recent finding that the age standardised mortality in patients with HeFH attending lipid clinics has now fallen to levels similar to that of the general population,³ whereas previously it was several fold increased.¹² General population screening for raised cholesterol, although increasingly being undertaken, is unlikely to lead to the recognition of many patients with HeFH before they develop CHD, because it is often not undertaken until middle age and then is often confined to patients who have other adverse cardiovascular risk factors, such as obesity, hypertension or diabetes, all of which are underrepresented in HeFH.⁷

The opportunity to detect HeFH by cholesterol measurement in patients with Achilles tendon pain, if more widely undertaken, could improve the detection rate of HeFH. Typically, in patients experiencing Achilles tendon pain the first episode occurred more than 20 years before referral to our lipid clinic. Our study showed that even in those patients referred to an orthopaedic clinic, cholesterol measurement was not done and when we consulted widely standard orthopaedic text books Achilles TX are generally described as “chronic Achilles tenosynovitis”, with no mention of cholesterol measurement for the investigation of either acute or chronic Achilles tendon pain.^{13–16}

One previous study has drawn attention to Achilles tenosynovitis as a presenting feature of HeFH,⁹ but this would appear to have had little impact on clinical practice. Our study suggests that Achilles tendon pain lasting 3 days or more is 6.75 times more likely to occur in patients with HeFH than in the general population (likelihood ratio). Severe Achilles tendon pain was sufficiently uncommon in the general population that it was not reported in our controls, but even if it is as prevalent as 1 in 100 to 1 in 1000, it would occur almost 40 to 400 times more commonly in HeFH. We cannot tell why some patients with HeFH are more susceptible to Achilles tendon pain than others. Although the serum cholesterol was similarly raised in patients who had remained free of any pain at presentation to our clinic, it is possible that earlier in life their cholesterol level had been lower than in those with Achilles tendon symptoms.

Achilles TX were first described at the end of the 19th century.^{17,18} Histologically in many respects they resemble advanced atheromatous lesions with cholesterol deposition both extracellularly and in the cytoplasm of histiocytic and other foam cells and an inflammatory cell infiltrate.¹⁹ There is

also a fibrous reaction (fig 2), which gives rise to their firmness and nodularity on palpation. The xanthomata are located deep within the tendon and cause it to become expanded when they may be detected by palpation, computed tomography²⁰ (fig 4), or magnetic resonance imaging.²¹ Imaging techniques are rarely needed, but our study shows that an attack of pain in the Achilles tendon region should signal the need for cholesterol measurement to exclude a diagnosis of HeFH.

Our study showed that in a small proportion of patients Achilles TX can be particularly disabling. Before statins were available, occasional reports suggested that cholesterol lowering treatment was associated with reduction in the size of Achilles TX.^{22,23} More recently, it has been our observation that they do resolve in patients compliant with statin treatment, meaning that surgery should rarely be required. It has, however, also been our observation and that of others (Thompson GR, personal communication) that exacerbations of Achilles tenosynovitis can occur when statin treatment is started, associated with rapid lowering of cholesterol. In patients with HeFH treated with partial ileal bypass,²⁴ this was also a frequent occurrence, which could cause a more generalised tenosynovitis even in sites where xanthomata had not previously been evident. Occasionally, such tenosynovitis is wrongly diagnosed as myositis and attributed to a side effect of statin treatment. The condition would seem to be akin to the exacerbations of gout, which occur when allopurinol treatment is begun and the serum uric acid level decreases rapidly. The mobilisation of cholesterol, like that of uric acid crystals, presumably provokes an inflammatory cell reaction.

We conclude that the wider recognition that HeFH is frequently associated with Achilles tenosynovitis would assist in its early diagnosis and in the management of both conditions

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