Heart and Vessels (2019) 34:1595–1599
https://doi.org/10.1007/s00380-019-01400-6

ORIGINAL ARTICLE

Prevalence of Achilles tendon xanthoma and familial hypercholesterolemia in patients with coronary artery disease undergoing percutaneous coronary intervention

Hideki Kitahara[1] · Naoto Mori[1] · Yuichi Saito[1] · Takashi Nakayama[1] · Yoshihide Fujimoto[1] · Yoshio Kobayashi[1]

Received: 28 October 2018 / Accepted: 5 April 2019 / Published online: 9 April 2019

Abstract
Familial hypercholesterolemia (FH) is reportedly associated with the development of coronary artery disease (CAD), especially acute coronary syndrome (ACS). However, the prevalence of FH in patients with stable CAD is still unclear. The aim of this study was to investigate the prevalence of Achilles tendon xanthoma (ATX) and heterozygous FH in patients with stable CAD and ACS undergoing percutaneous coronary intervention (PCI). A total of 423 patients with CAD (273 stable CAD and 150 ACS) undergoing PCI at Chiba University Hospital between June 2016 and February 2018 were enrolled in this study. Soft X-ray radiography of the Achilles tendon was performed in all patients, and a maximum thickness of 9 mm or more is regarded as ATX. Heterozygous FH was diagnosed according to the Japan Atherosclerosis Society Guidelines. In comparisons between stable CAD and ACS patients, ATX was observed in 9.2% vs. 15.3% ($p=0.055$), and heterozygous FH was diagnosed in 3.7% vs. 5.3% ($p=0.416$), respectively. Among ACS patients, those with ST elevation myocardial infarction (STEMI) showed the highest prevalence of ATX (19.5%) and FH (7.3%). Whereas ATX and heterozygous FH were considerably observed in patients with ACS, a certain number of ATX and heterozygous FH were also detected in stable CAD patients.

Keywords Coronary artery disease · Familial hypercholesterolemia · Achilles tendon xanthoma

Introduction

Although heterozygous familial hypercholesterolemia (FH) is one of the most common genetic disorders characterized by significantly high levels of plasma low-density lipoprotein (LDL) cholesterol, it has been reported that the majority of patients with heterozygous FH are underdiagnosed and undertreated in common clinical settings [1]. Heterozygous FH is well known to be associated with an increased risk of premature coronary artery disease (CAD) [2]. Therefore, previous studies have reported that the most common cause of death in heterozygous FH patients is CAD [3, 4]. Recently, the high prevalence of heterozygous FH in patients with acute coronary syndrome (ACS) was reported in a Japanese population [5]. However, little has been reported on the prevalence of heterozygous FH in patients with stable CAD. Since the number of stable CAD patients is usually greater than that of ACS patients [6], it should be crucial to detect the stable CAD patients with heterozygous FH, who require strict lipid management for secondary prevention of cardiovascular disease. Tendon xanthomas are well known to be highly specific for FH patients, and often emerge as Achilles tendon thickening [7]. For clinical diagnosis of heterozygous FH, measurement of Achilles tendon thickness by radiography is useful to detect tendon xanthoma, which is one of the diagnostic criteria for heterozygous FH proposed by the Japan Atherosclerosis Society (JAS) [8]. Thus, the aim of this study was to investigate the prevalence of Achilles tendon xanthoma (ATX) and heterozygous FH in patients with stable CAD and ACS undergoing percutaneous coronary intervention (PCI).

✉ Hideki Kitahara
hkitahara@chiba-u.jp

[1] Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan

Patients and methods

Study population

The patients with CAD undergoing PCI at Chiba university hospital between June 2016 and February 2018 were enrolled in this study. Among a total of consecutive 487 patients, 64 were excluded because of missing ATX data, or Achilles tendon thickening due to other reasons, such as sitosterolemia or a history of Achilles tendon rupture (Fig. 1). Consequently, 423 patients were eligible for this analysis. The institutional review boards at Chiba University Hospital approved this study, and all patients provided written informed consent.

Diagnosis of heterozygous FH

Heterozygous FH was diagnosed, if a patient meets 2 or 3 of the following criteria, according to the diagnostic criteria for heterozygous FH in adults proposed by JAS in 2017: (1) hyper-LDL cholesterolemia (an untreated LDL cholesterol level of > 180 mg/dL); (2) tendon xanthomas (tendon xanthoma on backs of the hands, elbows, knees, or elsewhere, or Achilles tendon thickening) or xanthoma tuberosum; and (3) family history of FH or premature CAD (within a patient's 2nd degree relatives) [8]. Plasma lipid levels were measured at hospital arrival before PCI in emergent PCI cases, and at hospital admission the day before PCI in elective PCI cases, regardless of food intake. If possible, previous data of lipid profiles before statin administration were obtained from medical records. LDL cholesterol level was usually measured by the direct method. LDL cholesterol test kit for measurement was from Kyowa Medex Co., Ltd. Tokyo, Japan. However, if LDL cholesterol level was not available, it was calculated using the Friedewald equation. Soft X-ray radiography of the Achilles tendon was performed, and a maximum thickness of 9 mm or more, excluding skin and subcutaneous tissue, is regarded as ATX. Measurements of Achilles tendon thickness in 40 randomly selected patients by 2 observers, and by 1 observer at 2 separate sessions, showed an interobserver correlation coefficient of 0.971 and an intraobserver coefficient of 0.985. Family history of premature CAD was defined by onset at less than 55 years old for men and at less than 65 years old for women.

Definition of CAD

CAD was categorized as stable CAD, including stable angina and silent myocardial ischemia, and ACS. ACS was further categorized as ST elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTE-ACS) according to the universal definition [9]. In patients who received multiple PCI during the study period, clinical presentation at the first PCI was adopted for patient's baseline characteristics.

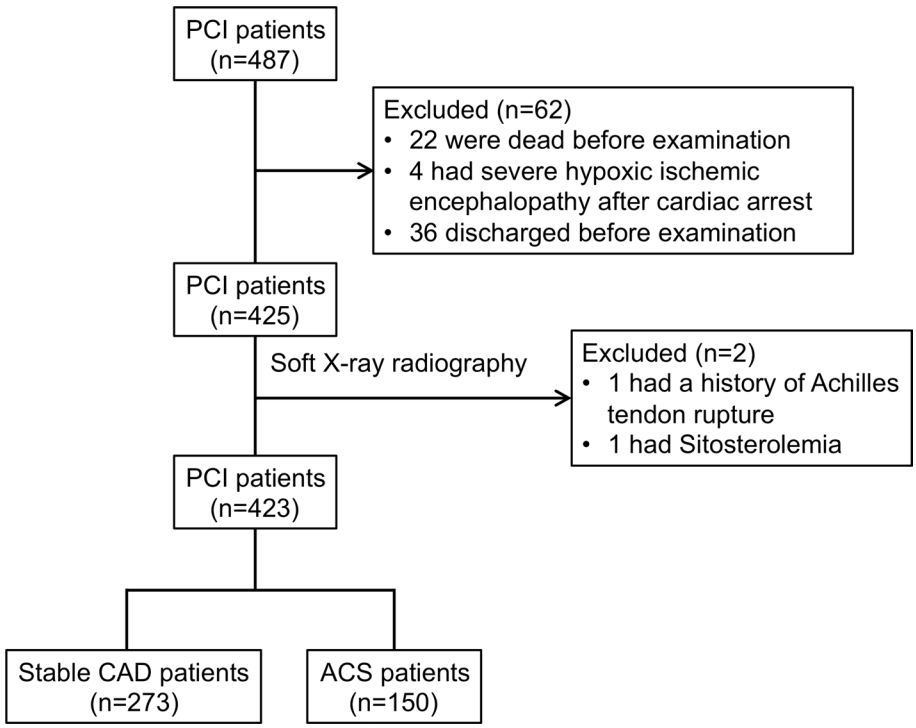

Fig. 1 Flowchart of patient population. *ACS* Acute coronary syndrome, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention

Statistical analysis

Statistical analysis was performed using JMP® 13.0 (SAS Institute, Cary, NC). Categorical variables are presented as percentages, and compared using Chi-square test or Fisher's exact test. Continuous variables are presented as mean ± SD. Comparisons between 2 continuous variables were done with a 2-tailed, unpaired *t* test. Achilles tendon thickness among the 3 groups was compared using analysis of variance (ANOVA) with a post hoc comparison using the Tukey's honestly significant difference test. A nominal *p* value of <0.05 was considered statistically significant.

Results

Out of 423 patients enrolled, 273 (64.5%) presented with stable CAD, while 150 (35.5%) presented with ACS, including 41 (9.7%) STEMI and 109 (21.8%) NSTE-ACS, at the first PCI during the study period. Clinical characteristics between stable CAD and ACS groups are shown in Table 1. The stable CAD group tended to have the higher percentage of male and greater body mass index, and showed significantly less number of PCI during the study period, compared to the ACS group. Total and LDL cholesterol levels were significantly higher in ACS patients than in stable CAD patients, whereas prior statin administration was more frequent in stable CAD patients than in ACS patients. Compared to the stable CAD patients, Achilles tendon thickness was significantly greater in ASC patients (6.9 ± 1.6 vs. 7.7 ± 2.0, $p<0.001$). Although 11 out of 423 (2.6%) patients had no information of family history of premature CAD or FH, there was no difference in its prevalence between stable CAD and ACS patients (Table 1). LDL cholesterol level was comparable between the patients with and without information of family history (111.6 ± 37.1 vs. 103.1 ± 18.3, $p=0.449$).

Overall, 11.4% of patients showed ATX and 4.3% were diagnosed as heterozygous FH (Table 2). In stable CAD patients, 9.2% had ATX and 3.7% were heterozygous FH, whereas 15.3% had ATX and 5.3% were heterozygous FH in ACS patients ($p=0.055$ and $p=0.416$ between stable CAD and ACS patients, respectively). In STEMI patients, especially 19.5% had ATX and 7.3% were heterozygous FH.

In terms of age, lipid profiles, and statin administration, the comparison was conducted between ATX and non-ATX patients (Table 3), and between FH and non-FH

Table 1 Baseline clinical characteristics

	Stable CAD ($n=273$)	ACS ($n=150$)	*p*
Age (years)	68.8 ± 10.3	69.4 ± 10.3	0.553
Male gender (%)	81.0	73.3	0.069
BMI (kg/m^2)	24.5 ± 3.9	23.8 ± 3.1	0.071
Hypertension (%)	72.9	70.7	0.625
Dyslipidemia (%)	63.0	68.7	0.243
Diabetes (%)	44.7	42.0	0.594
Current smoker (%)	15.5	16.8	0.732
Family history of CAD (%)	27.8	32.4	0.318
Family history of premature CAD or FH (%)	7.6	7.4	0.935
Prior myocardial infarction (%)	17.6	14.7	0.440
Prior CABG (%)	7.0	6.7	0.909
Prior PCI (%)	34.4	26.7	0.101
Multivessel disease (%)	67.0	64.0	0.529
Number of PCI received during the period	1.1 ± 0.4	1.2 ± 0.5	0.007
eGFR (mL/min/1.73 m^2)	64.9 ± 18.7	63.8 ± 23.2	0.631
Hemodialysis (%)	5.9	4.0	0.410
Ejection fraction (%)	56.0 ± 12.5	53.8 ± 12.7	0.101
Total cholesterol (mg/dL)	176.2 ± 40.2	189.2 ± 41.3	0.002
LDL cholesterol (mg/dL)	107.6 ± 36.4	118.8 ± 36.2	0.003
HDL cholesterol (mg/dL)	52.3 ± 15.1	50.9 ± 15.8	0.361
Triglycerides (mg/dL)	151.9 ± 82.0	146.3 ± 92.9	0.522
Statin administration (%)	55.7	34.9	<0.001
Achilles tendon thickness (mm)	6.9 ± 1.6	7.7 ± 2.0	<0.001

BMI body mass index, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *eGFR* estimated glomerular filtration rate, *FH* familial hypercholesterolemia, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *PCI* percutaneous coronary intervention

Table 2 Prevalence of ATX and heterozygous FH

	ATX (%)	Heterozygous FH (%)
Overall	11.4	4.3
Stable CAD	9.2	3.7
ACS	15.3	5.3
NSTE-ACS	13.8	4.6
STEMI	19.5	7.3

CAD coronary artery disease, *ACS* acute coronary syndrome, *ATX* Achilles tendon xanthoma, *FH* familial hypercholesterolemia, *NSTE-ACS* non-ST elevation ACS, *STEMI* ST elevation myocardial infarction

Table 3 Comparison of ATX and non-ATX patients

	ATX ($n=48$)	Non-ATX ($n=375$)	p
Age (years)	67.9 ± 8.9	69.2 ± 10.4	0.407
Total cholesterol (mg/dL)	182.3 ± 55.5	180.6 ± 38.9	0.778
LDL cholesterol (mg/dL)	116.1 ± 47.8	110.8 ± 35.1	0.353
HDL cholesterol (mg/dL)	47.0 ± 16.3	52.4 ± 15.2	0.024
Triglycerides (mg/dL)	136.1 ± 84.6	151.7 ± 86.0	0.237
Statin administration (%)	68.8	45.7	0.003

ATX Achilles tendon xanthoma, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Table 4 Comparison of FH and non-FH patients

	FH ($n=18$)	Non-FH ($n=405$)	p
Age (years)	65.6 ± 9.0	69.2 ± 10.3	0.142
Total cholesterol (mg/dL)	205.4 ± 70.4	179.7 ± 39.0	0.009
LDL cholesterol (mg/dL)	136.5 ± 61.0	110.3 ± 61.0	0.004
HDL cholesterol (mg/dL)	49.9 ± 20.1	51.9 ± 15.2	0.606
Triglycerides (mg/dL)	163.1 ± 107.7	149.4 ± 84.9	0.507
Statin administration (%)	70.6	47.4	0.061

FH familial hypercholesterolemia, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

patients (Table 4). There were no significant differences in lipid profiles except for HDL cholesterol, while the rate of statin administration was significantly higher in ATX patients compared to non-ATX patients. Between FH and non-FH patients, total cholesterol and LDL cholesterol levels were significantly higher in FH patients, although the rate of statin administration tended to be higher in FH patients compared to non-FH patients.

Discussion

The present study demonstrated that, whereas ATX and heterozygous FH were considerably observed in patients with ACS, a certain number of ATX and heterozygous FH were also detected in stable CAD patients. In addition, approximately 1 in 3 patients with ATX were diagnosed as heterozygous FH.

Heterozygous FH is associated with an increased risk of premature CAD. Previously, the prevalence of heterozygous FH in patients with ACS was reported in several reports. In the EUROASPIRE IV study, the prevalence of potential FH diagnosed using the Dutch Lipid Clinic Network Criteria in patients with acute coronary events was 8.3% in European countries [10]. Recently, a multicenter Japanese registry demonstrated that 5.7% of ACS patients were diagnosed as heterozygous FH [5]. On the other hand, there are few studies reporting the prevalence of heterozygous FH in patients with stable CAD, although the number of stable CAD patients is usually greater than that of ACS patients [6]. In the present study, a certain number of heterozygous FH was detected in stable CAD patients, although its prevalence did not reach that of ACS patients. It should be quite important to identify heterozygous FH in stable CAD patients as well as ACS patients, who require strict lipid management for secondary prevention of cardiovascular disease.

Tendon xanthoma is strongly associated with a genetic diagnosis and highly specific for FH patients [11]. For clinical diagnosis of heterozygous FH, tendon xanthoma, represented as Achilles tendon thickness, is one of the important diagnostic criteria for FH proposed by JAS and the Simon Broome criteria, because of its high sensitivity and specificity [8, 12]. Since Achilles tendon thickness can be easily measured using soft X-ray radiography, it should be more proactively introduced in clinical settings of CAD to detect heterozygous FH. On the other hand, it has been reported that there are some FH patients without xanthoma [7]. Thus, it is also important to keep in mind that the absence of xanthoma does not necessarily contradict FH diagnosis.

As previously reported, there is a considerable number of ACS patients with ATX who do not meet the diagnostic criteria for heterozygous FH [5, 13]. While it is potential that heterozygous FH might be actually included in such patients, they could not be clinically diagnosed as heterozygous FH, possibly due to the lowered and masked LDL cholesterol level and/or lack of detailed family history of premature CAD and FH. In the present study, 55% of stable CAD patients and 33% of ACS patients were already on statin therapy. Furthermore, temporal reduction of LDL cholesterol level after onset of ACS has been previously reported [14, 15]. In addition,

while it is certainly helpful to collect information about family history for diagnosis of FH, there are often difficulties in obtaining the complete information. Therefore, clinical diagnostic performance of the existing criteria might have limitations on their accuracy. Although genetic examination would be useful to clarify diagnosis of FH in such patients, generalization of genetic examination is costly and impractical in common clinical settings. As measurement of Achilles tendon thickness can be easily conducted, it may be a good screening method to detect heterozygous FH. Even if the patients were not diagnosed as heterozygous FH, the CAD patients with ATX should probably undergo careful treatment with intensive lipid lowering therapy [16], despite the type of CAD presentation.

There were several limitations in the present study. First, sample size was relatively small, especially in STEMI patients. Considering that the sensitivity of ATX is not so high [7], the estimated frequency of heterozygous FH might be too high in STEMI patients. The rate of ATX and heterozygous FH in STEMI patients should be further investigated in a larger patient population. Second, untreated LDL cholesterol level was unknown in some patients on statin therapy. Third, genetic molecular analysis was not performed to identify monogenic mutations associated with FH. Therefore, it was unclear how many patients with ATX who did not meet the clinical diagnostic criteria for heterozygous FH were genetically diagnosed as heterozygous FH.

Conclusion

Whereas ATX and heterozygous FH were considerably observed in patients with ACS, a certain number of ATX and heterozygous FH were also detected in stable CAD patients.

Acknowledgements This study was not funded by any organizations or sponsors.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Boren J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A (2013) Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 34:3478–3490a
2. Mabuchi H, Koizumi J, Shimizu M, Takeda R (1989) Development of coronary heart disease in familial hypercholesterolemia. Circulation 79:225–232
3. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierod MB, Leren TP, Retterstol K (2014) Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992–2010. J Am Heart Assoc 3:e001236
4. Krogh HW, Mundal L, Holven KB, Retterstol K (2016) Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death. Eur Heart J 37:1398–1405
5. Ohmura H, Fukushima Y, Mizuno A, Niwa K, Kobayashi Y, Ebina T, Kimura K, Ishibashi S, Daida H (2017) Estimated prevalence of heterozygous familial hypercholesterolemia in patients with acute coronary syndrome. Int Heart J 58:88–94
6. Inohara T, Kohsaka S, Yamaji K, Amano T, Fujii K, Oda H, Uemura S, Kadota K, Miyata H, Nakamura M (2017) Impact of institutional and operator volume on short-term outcomes of percutaneous coronary intervention: a report from the Japanese Nationwide Registry. JACC Cardiovasc Interv 10:918–927
7. Bujo H, Takahashi K, Saito Y, Maruyama T, Yamashita S, Matsuzawa Y, Ishibashi S, Shionoiri F, Yamada N, Kita T (2004) Clinical features of familial hypercholesterolemia in Japan in a database from 1996–1998 by the research committee of the ministry of health, labour and welfare of Japan. J Atheroscler Thromb 11:146–151
8. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, Umemoto S, Egusa G, Ohmura H, Okamura T, Kihara S, Koba S, Saito I, Shoji T, Daida H, Tsukamoto K, Deguchi J, Dohi S, Dobashi K, Hamaguchi H, Hara M, Hiro T, Biro S, Fujioka Y, Maruyama C, Miyamoto Y, Murakami Y, Yokode M, Yoshida H, Rakugi H, Wakatsuki A, Yamashita S (2018) Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb 25:846–984
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD (2012) Third universal definition of myocardial infarction. J Am Coll Cardiol 60:1581–1598
10. De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein JJ, Kotseva K, Ray K, Reiner Z, Wood D, De Bacquer D (2015) Prevalence and management of familial hypercholesterolaemia in coronary patients: an analysis of EUROASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis 241:169–175
11. Civeira F (2004) Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 173:55–68
12. Scientific Steering Committee on behalf of the Simon Broome Register Group (1991) Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 303:893–896
13. Harada T, Inagaki-Tanimura K, Nagao M, Sato Y, Sudo M, Okajima F, Sugihara H, Oikawa S (2017) Frequency of Achilles Tendon xanthoma in patients with acute coronary syndrome. J Atheroscler Thromb 24:949–953
14. Rosenson RS (1993) Myocardial injury: the acute phase response and lipoprotein metabolism. J Am Coll Cardiol 22:933–940
15. Wattanasuwan N, Khan IA, Gowda RM, Vasavada BC, Sacchi TJ (2001) Effect of acute myocardial infarction on cholesterol ratios. Chest 120:1196–1199
16. Tanaka S, Ikari Y, Ijichi T, Nakazawa G (2017) Treat-to-target lipid control is effective but highlighted poor prognosis without indication of statin following percutaneous coronary intervention. Cardiovasc Interv Ther 32:358–364