Eyelid Plaque May Signal Severe Atherosclerosis

BY KERRI WACHTER

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Plaque occurring around the eyelids may offer clinicians a new way of identifying patients at an increased risk for myocardial infarction and severe atherosclerosis, a study has shown.

"The results from this study suggest that xanthelasmata are a cutaneous marker of atherosclerosis independent of lipid concentrations and thus should be considered in clinical practice as an independent and additional risk factor for myocardial infarction and ischemic heart disease," Mette Christoffersen and her coinvestigators wrote in a study published online (BMJ 2011;343:d5497).

The presence of xanthelasmata predicted MI (hazard ratio, 1.48); ischemic heart disease (HR, 1.39); severe atherosclerosis determined by ankle brachial index (HR, 1.69); and death (HR, 1.14), in a Danish population-based study of 12,745 patients. However, on multifactorial adjustment for arcus corneae, no hazard ratios remained significant. The presence of both xanthelasmata and arcus corneae significantly increased the risk of ischemic heart disease (HR, 1.56) but not any other outcomes after multifactorial adjustment.

Xanthelasmata palpebrarum are sharply demarcated, yellowish flat plaques that appear on the upper or lower eyelids, most often near the inner canthus. Xanthelasmata represent areas of macrophages containing lipids. Arcus corneae (or arcus senilis) is a gray-white-yellowish opacity that is located near the periphery of the cornea, though separated from the limbic margin by a clear corneal zone. Arcus corneae represents deposits of cholesteryl ester–rich lipid particles. It has been suggested that xanthelasmata and arcus corneae may be markers of proatherogenic changes in the vessels and thus markers of atherosclerosis.

> 'Presence of xanthelasmata in itself predicts risk of myocardial infarction, ischemic heart disease, severe atherosclerosis, and death … independent of well-known' risk factors.

"The findings from our study could be of particular value in societies where access to laboratory facilities, and thus lipid profile measurement, is difficult. In this setting, presence of xanthelasmata may be a useful predictor of underlying atherosclerotic disease. An easy registration of presence of xanthelasmata along with age and sex makes it possible to assess the risk of myocardial infarction and ischemic heart disease and thus to make sure that people at increased risk are managed accordingly with lifestyle changes and treatment to reduce low-density lipoprotein cholesterol," wrote Ms. Christoffersen, a clinical biochemistry PhD student at Rigshospitalet in Copenhagen, and her colleagues.

They used data from the Copenhagen City Heart Study, which is a prospective cardiovascular study of the Danish general population that started in 1976-1978 with follow-up examinations. A total of 19,329 white women and men of Danish descent were drawn randomly from the Copenhagen Central Person Registry and invited to participate. Data came from a self-administered questionnaire, a physical examination, and blood samples.

For this analysis, the researchers included 12,745 people, for whom complete information on all relevant variables, including xanthelasmata and arcus corneae, were available at baseline. The patients were followed from baseline at the 1976-1978 examination to the end of May 2009 through the use of their unique Central Person Register number. No participants were lost to follow-up.

Trained nurses or medical laboratory technicians determined the presence of xanthelasmata and arcus corneae by careful visual inspection of the eyelids and the cornea during the physical examination. The investigators collected and verified diagnoses of MI and ischemic heart disease using ICD-8 and ICD-10 codes by reviewing all hospital admissions, diagnoses entered in the national Danish Patient Registry, all causes of death entered in the national Danish Causes of Death Registry, and medical records from hospitals and general practitioners.

The prevalence of xanthelasmata was 4.4% and similar in women and men. The prevalence of arcus corneae was 24.8% overall, but was lower in women than in men (20.1% vs. 30.2%), Ms. Christoffersen and her associates said.

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Patients who have xanthelasmata palpebrarum (shown above) may require more aggressive management of their cardiovascular risk factors.

Potential patients with ischemic cerebrovascular disease, including ischemic stroke, were collected from the national Danish Patient Registry and the national Danish Causes of Death Registry. Hospital records were reviewed by experienced neurologists. Ankle brachial index, a drop in blood pressure in the legs that predicts severe atherosclerosis, was determined in the 2001-2003 examination of the Copenhagen City Heart Study in 2,773 participants, who had also participated in the baseline examination and had complete information on all relevant variables, including xanthelasmata and arcus corneae.

Enzymatic methods were used on fresh plasma samples to measure plasma concentrations of total cholesterol, triglycerides, and high-density lipoprotein cholesterol, the last after precipitation of lipoproteins that contained apolipoprotein B.

The median follow-up was 22 years. In all, 1,872 participants developed MI, 3,699 developed ischemic heart disease, 1,498 developed ischemic strokes, 1,815 developed ischemic cerebrovascular disease, and 8,507 died.

The models were adjusted for age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes, pack-years of smoking, alcohol consumption, physical activity, postmenopausal status, hormone therapy, education, income, and family history of ischemic vascular disease.

In this population, the "presence of xanthelasmata in itself predicts risk of myocardial infarction, ischemic heart disease, severe atherosclerosis, and death in the general population independent of well-known cardiovascular risk factors, including plasma cholesterol and triglyceride concentrations. In contrast, arcus corneae is not an important independent predictor of risk," the authors concluded. ∎

VIEW ON THE NEWS

Findings Are Boon to Clinicians

In an accompanying editorial, Dr. Antonio B. Fernandez and Dr. Paul D. Thompson discussed the clinical relevance of the findings.

"In the linked prospective cohort study, Christoffersen and colleagues assess whether xanthelasmata and arcus corneae, individually and combined, predict risk of ischemic vascular disease and death in the general population," Dr. Fernandez and Dr. Thompson wrote, noting that there are some good reasons for suspecting such a link (BMJ 2011;343:d5304).

"Both xanthelasmata and arcus corneae are composed of cholesteryl esters similar to those found in serum low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol. They share similar risk factors and have pathophysiological similarities with atherosclerosis," they noted.

Importantly, the results of this study confirm "that xanthelasmata are an important predictor of cardiovascular disease events and death beyond [their] known association with hyperlipidemia."

However, "what do these results mean in practice?" they asked. "Overall, the evidence highlights the importance of a comprehensive physical examination and suggests that xanthelasmata could be used by general clinicians to help identify people at higher risk of cardiovascular disease. These people may have an enhanced biological propensity to deposition of cholesterol in vascular and soft tissue, which is not fully represented by their fasting lipid profiles. … Patients with xanthelasmata may therefore require more aggressive management of risk factors," they concluded.

DR. FERNANDEZ is a clinical cardiology fellow at Brown University in Providence, R.I. Dr. Thompson is the director of cardiology at Hartford (Conn.) Hospital. DR. THOMPSON reported significant financial relationships with several pharmaceutical companies.