Acute Coronary Syndrome With or Without Heterozygous Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is the most critical and commonly inherited cause of premature coronary artery disease (CAD) because it results in long-term exposure to higher lipid levels. Heterozygous FH is seen in approximately 1 in every 500 people, and homozygous FH is observed in about 1 in every 1 million people in Japan. A diagnosis of FH can be performed clinically (by history, clinical examination, and measurement of the serum lipid profile) or by genetic molecular analysis. According to the 2012 Japan Atherosclerosis Society (JAS) Guidelines, the diagnostic criteria for heterozygous FH are 2 or more of the following: 1) serum low-density lipoprotein cholesterol (LDL-C) > 180 mg/dL, under no treatment, 2) tendon/skin xanthoma(s), and 3) family history of FH or premature CAD within second-degree relatives.

Among patients with acute coronary syndrome (ACS), it is essential to control cholesterol levels in those with heterozygous FH. However, the percentage of ACS patients who have heterozygous FH is not yet clear. To address this question, in this issue of International Heart Journal, Ohmura, et al reported the prevalence of heterozygous FH among patients with ACS by measuring achilles tendon thickness (ATT) according to the diagnostic criteria for heterozygous FH in adults in the 2012 JAS Guidelines. They examined the clinical characteristics of 296 patients with ACS with and without heterozygous FH in a multicenter registration study. They found that 53 patients (17.9%) had an ATT of 9 mm or more. These patients were significantly younger and had significantly higher LDL-C levels than patients with ATT less than 9 mm. The prevalence of heterozygous FH was 5.7%, and was higher in patients less than 60 years old (7.8%). One in 3.5 patients with ATT of 9 mm or more satisfied the criteria for heterozygous FH.

Coronary risk factors accelerate the development of atherosclerosis and must be treated aggressively, especially in patients with FH. In this study, no significant differences in other coronary risk factors, specifically gender or the percentage of statin treatment, were observed between patients with ATT of 9 mm or more and those with ATT less than 9 mm. An ATT of 9 mm or more is an important risk factor. Thus, we should consider measuring ATT in patients with dyslipidemia, especially those with a family history of FH or premature CAD within second-degree relatives, before the onset of ACS.

There is another important issue regarding aggressive lipid-lowering therapy in patients with heterozygous FH before and after ACS. Statins are used as first-line drugs in patients with FH. There is a therapeutic gap and a high recurrence rate of cardiac events during long-term follow-up. Although the LDL-C level for patients with secondary prevention and/or FH is less than 100 mg/dL according to the 2012 JAS Guidelines, patients with FH must be treated using combinations of lipid-lowering drugs under the care of specialists. In this respect, an additional therapeutic option is now available, which entails the use of proprotein convertase subtilisin/Kexin 9 (PCSK9) inhibitors. PCSK9 inhibitors block the binding of PCS-9 with LDL receptors and prevent the degradation of LDL receptors. In the GLAGOV randomized clinical trial, in patients with angiographic CAD, the LDL-C level after 76 weeks of treatment was 36.6 mg/dL in the evolocumab group versus 93.0 mg/dL in the placebo group (P < 0.001). The primary outcome, the nominal change in percent atheroma volume at 78 weeks, was -0.95% in the evolocumab group versus 0.05% in the placebo group (P < 0.001 for between-group comparison). The inhibitors have excellent lipid-lowering properties and may have a beneficial effect on the outcome of CAD in patients with FH.

The study of Ohmura, et al has several limitations, as they noted. There was some possibility of underdiagnosing heterozygous FH in patients with ACS because they found a considerable number of patients with ATT of 9 mm or more without diagnosing heterozygous FH. In addition, they did not perform a genetic molecular analysis to identify monogenic mutations that were associated with FH.

In conclusion, the findings of Ohmura, et al demonstrate both the usefulness of measuring ATT and the high prevalence of heterozygous FH in patients with ACS. We emphasize the need to clinically recognize ATT of 9 mm or more and the possibility of the familial inheritance of FH with elevated LDL-C. Early diagnosis and early initiation of lipid-lowering therapy may save individual patients and their family members. In addition, FH should be suspected in premature CAD patients with high serum LDL-C levels.

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DISCLOSURE

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