Consider Cardiomyopathy in Subjects With Familial Partial Lipodystrophy

To the Editor:

Hegele\(^1\) excellently described the presence of premature coronary artery disease in 8 out of 23 adult subjects (aged above 35 years) with familial partial lipodystrophy (FPL) carrying \(\text{LMNA}\) mutations. His intriguing observations underline the striking similarity between FPL and the metabolic syndrome (also called syndrome X). The latter is known to result in premature coronary artery disease. In FPL, the phenotype of altered fatty tissue distribution and the prominence of the skeletal muscles, especially of the lower limbs, precedes the manifestation of dyslipidemia and diabetes mellitus. Dyslipidemia in turn seems to occur many years before diabetes mellitus may occur.\(^2\) However, it is remarkable that Hegele reported on insulin resistance in all studied subjects, although 18/23 had dyslipidemia and 12/23 had diabetes mellitus. Does hyperinsulinemia and insulin resistance, respectively, precede dyslipidemia and diabetes mellitus in this selected cohort of patients? The observed coronary artery disease in FPL carrying \(\text{LMNA}\) mutations is presumably caused by the cardiovascular risk factors, which develop over time. At this point, there is no evidence that \(\text{LMNA}\) mutations result directly in atherogenesis.

Most of the currently reported mutations within \(\text{LMNA}\) result in peripheral and/or cardiac myopathy and/or atriовentricular conduction disease, but not in FPL.\(^3\) In contrast, mutations within \(\text{LMNA}\) causing FPL have not been observed to result in peripheral or cardiac muscle dystrophy. However, subjects with FPL present with prominent skeletal muscles with no adequate gain in muscular function. There is no detailed information on the heart in affected subjects.\(^4\) We identified an FPL family carrying the R482W mutation in respect to the genesis of cardiomyopathy in the R482W mutation. The 36-year-old female index patient and her 33-year-old brother complained of exercise-induced tachycardia. Both had the classical phenotype with lipodystrophy, peripheral muscle hypertrophy, insulin resistant diabetes mellitus, and severe hypertriglyceridemia (hyperlipoproteinemia type V). We detected no atherosclerosis by ultrasound of the carotids and abdominal aorta, echocardiography, and coronary artery catheterization including intravascular ultrasound. Subsequently, we screened relatives and identified an affected 46-year-old male subject presenting with a moderate lipodystrophic habitus, insulin resistant diabetes mellitus, and hyperlipoproteinemia type IV. Most interestingly, this patient had a history of chronic atrial fibrillation. Subsequent echocardiography and cardiac catheterization showed dilated cardiomyopathy (ejection fraction 43%) without any atherosclerotic lesion. The search for coexisting risk factors yielded solely a daily alcohol consumption of 20 to 40 g. This observation of a potential role of alcohol consumption or other unidentified factors in the presence of the R482W mutation in respect to the genesis of cardiomyopathy needs further evaluation.

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Response

Dr Schmidt’s letter raises several interesting points. First, what is the chain of metabolic events in Dunnigan-type familial partial lipodystrophy (FPLD) that begins with mutant \(\text{LMNA}\) and ends with premature atherosclerosis? The temporal sequence is suggested by observations from Canadian FPLD kindreds, in which relatively large numbers of mutation carriers were assessed at various ages and stages of disease progression.\(^1,2\) The initial metabolic abnormality is hyperinsulinemia, reflecting insulin resistance, although whether this precedes, overlaps with, or follows the adipose repartitioning is unclear. The next abnormality to present is dyslipidemia: elevated triglycerides and low HDL cholesterol. Hypertension presents next, although this is more variable. Finally, fasting hyperglycemia—frank diabetes—occurs many years later and most likely reflects pancreatic \(\beta\)-cell failure in the context of chronic insulin resistance. Dr Schmidt correctly states that \(\text{LMNA}\) mutations do not directly produce atherosclerosis; carriers with coronary heart disease (CHD) end points had hyperinsulinemia, dyslipidemia, hypertension, and diabetes.\(^3\) These intermediate metabolic traits—all potent risk factors—certainly led to the CHD in carriers.\(^3\) What is the cellular basis for these deleterious traits in carriers? Is the adipose repartitioning the inciting event in the cascade? These questions await resolution by other in vivo and in vitro experiments.

Dr Schmidt next raised the issue of overlap between lipodystrophy and other disorders due to \(\text{LMNA}\) mutations, such as cardiomyopathy. In general, the association between the affected tissue-type and the specific mutated \(\text{LMNA}\) residue is remarkably specific.\(^4\) For instance, lipodystrophy almost never occurs together with myopathy; none of the Canadian FPLD patients had either cardiomyopathy or conduction disturbances.\(^3\) The heart disease was clearly atherosclerotic, as indicated by coronary artery bypass graft surgery.\(^3\) However, some of us have seen rare patients, such as the one described by Dr Schmidt, with an overlap of lipodystrophy and cardiomyopathy. Elucidating the molecular mechanisms of these overlap syndromes will be very interesting.

Finally, Dr Schmidt suggested that gene-environment interactions could modulate the phenotype in carriers of mutant \(\text{LMNA}\). This appears to be true for atherosclerosis susceptibility. For example, an elderly subject with definite FPLD and the \(\text{LMNA}\) R482W mutation escaped the development of diabetes, dyslipidemia, hypertension, and CHD.\(^5\) Her most obvious protective factor was a lifelong history of daily 5-km walks, suggesting that lifestyle could attenuate the metabolic complications. If confirmed, such observations could have therapeutic implications for FPLD mutation carriers who are identified early in the course of their disease.

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Circulation. 2002;105:e7
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
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