ABNORMALITIES OF APOLIPOPROTEIN B METABOLISM

IN THE LIPID CLINIC

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Abstract: Apolipoprotein (apo) B-100 is the main protein component of low density lipoprotein (LDL) and plays a crucial role in cholesterol and lipoprotein metabolism. Elevated LDL cholesterol concentrations may derive either from a defective clearance of LDL or from a reduced removal. In the present report two apo B abnormalities that cause hypercholesterolemia were investigated. The case of a family affected with defective apo B-100 and of a woman with severe hypercholesterolemia and hyper-apobetalipoproteinemia are presented.

INTRODUCTION

Apolipoprotein (apo B), the main protein constituent of low density lipoprotein (LDL), very low density lipoprotein (VLDL) and chylomicrons, plays a pivotal role in lipoprotein metabolism (1). Apo B occurs naturally in two closely related forms (apo B-100 and B-48), encoded by the same gene (2). Apo B-100 is synthesized by the liver and is required for the assembly and secretion of VLDL. Apo B-48 is associated mainly with chylomicrons, chylomicron remnants and, in humans, it is believed to be synthesized solely by the intestine (1). The complete aminoacid (aa) sequence of human apo B was recently deduced from cDNA (3,4). Apo B-100 consists of a 4536 aa single polypeptide chain, apo B-48 represents the amino-terminal 47% of apo B. In humans apo B-100 is the predominant, if not exclusive, protein constituent of LDL, a lipoprotein that carries about 70% of plasma cholesterol, and is responsible for the receptor-mediated catabolism of LDL (5). The importance of LDL apo B-100/LDL receptor interaction in maintaining cholesterol homeostasis is best illustrated by familial hypercholesterolemia (FH), a genetic disease in which a defective
LDL receptor expression triggers an increase of plasma LDL cholesterol levels and premature coronary heart disease (CHD) (5).

Most individuals with hypercholesterolemia, however, possess a normal number of LDL receptors (6). Therefore, in most hypercholesterolemic patients other factors must contribute to the increased plasma levels of LDL, such as defective clearance or increased production.

In principle, elevated LDL concentrations that result from an inefficient clearance of LDL, may derive either from receptor or ligand defects. Genetic abnormalities of apo B-100, resulting in a decreased "in vitro" binding of LDL to their receptor, and hence a reduced "in vivo" catabolism of LDL, have been recently identified in some hypercholesterolemic patients (7-8). This genetic disease has been named familial defective apo B-100 (FDB) (7-9). In the families described so far, a single substitution at base 11039 (G to A) leads to an arginine to glutamine change in a mature protein at aa 3500. An overproduction of LDL may derive either from an increased synthesis of apo B-containing lipoproteins or from a decreased uptake of VLDL remnants thus allowing for a more efficient conversion of VLDL to LDL (6). Cases of this type or of with similar clinical and biochemical pattern may be frequently encountered in the activity of a lipid clinic.

In this report, we focus on the case of a family affected with FDB and on that of a middle age woman with a significant overproduction of apo B-containing lipoproteins.

SUBJECTS AND METHODS

Subjects

The cases of a family and of a woman presenting with hypercholesterolemia were investigated.
I) P. family
The proband (P.D.) was referred to us because of hypercholesterolemia at age of 10 yr (298 mg/dl); all other laboratory tests, including plasma triglycerides, glucose, IRI and T3 were within normal range. He had no xanthomas, xanthelasmas or thickening of the Achilles tendon. He is currently aged 16, in good health and consuming a low fat, low cholesterol diet. Upon screening of the family members, hypercholesterolemia was detected in the proband's father (P.V.), grandfather (P.At.), great-uncle (P.Al.) and great-aunt (P.W.) (Fig. 1).
II) Patient S.L.
The patient (S.L.), a 52 year old woman, was referred to us in September 1987, because of marked hypercholesterolemia with extensive xanthomata at the elbows, Achilles tendons, hands and fingers
At the first examination, the patient had a serum total cholesterol concentration of 658 mg/dl. Coronary arteriography showed complete occlusion of the right coronary, and severe stenosis of the left main (80%), anterior descending (90%) and circumflex (60%). In spite of the clearcut features of FH, elevated serum cholesterol or coronary artery disease were not reported in any of the first degree relatives.
Since October 1988, the pt has been treated with a