Research Article

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An Increased Risk of Coronary and Peripheral Vascular Disease Is Associated With Dysbetalipoproteinemia.

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ABSTRACT

Context : Apolipoprotein E malfunction caused by a genetic mutation in combination with other metabolic variables results in residual lipoproteins building up in the plasma, a condition known as dysbetalipoproteinemia (DBL). An elevated risk of peripheral vascular disease and coronary heart disease (PVD) has been noted in these patients in research conducted in the past.

Comparing the incidence of PVD and atherosclerotic cardiovascular disease (ASCVD) in a cohort of patients with DBL to normolipidemic controls was the main goal of the study. The incidence of PVD and ASCVD was compared between individuals with familial hypercholesterolemia (FH) and patients with DBL as a secondary goal.

Methods : The study comprised 1481 normolipidemic controls, 725 patients with FH, and 221 patients with DBL. Medical records were examined in order to gather the data.

Results : Compared to normolipidemic controls, patients with DBL had an overall increased risk of PVD (hazard ratio [HR] 13.58, 95% CI 4.76-38.75) and ASCVD (HR 3.55, 95% CI 2.17-5.83) (P<.0001). Patients with DBL showed an elevated risk of PVD (HR 3.89, 95% CI 1.20-12.55, P=.02) in comparison to those with FH.

conclusion : we showed that compared to normolipidemic controls, DBL patients have >3-fold and >13-fold greater risks of ASCVD and PVD, respectively. Moreover, DBL has a roughly 4-fold higher risk of PVD than FH. In order to enhance the clinical management of these patients by halting the progression of ASCVD, adequate DBL screening is essential.

Keywords : dysbetalipoproteinemia, cardiovascular disease, peripheral vascular disease, remnant, dyslipidemia, familial hypercholesterolemia

INTRODUCTION

The illness known as dysbetalipoproteinemia (DBL), also known as type III hyperlipoproteinemia, is linked to a pathological buildup of residual lipoproteins in the plasma that are high in cholesterol and triglycerides (TGs). A hereditary mutation in the apolipoprotein E (APOE) gene that results in a defective apoE protein and secondary variables such obesity, diabetes, metabolic syndrome, or insulin resistance are required for the development of DBL (1). Possession of the Є2Є2 genotype is the most common cause of apoE malfunction. Due to its poor affinity for the low-density lipoprotein (LDL) receptor, the apoE2 ligand is linked to a decreased clearance of lipoprotein remnants, including chylomicron remnants and intermediate-density lipoprotein.Due to the metabolic impact needed to initiate the disease, DBL primarily manifests in adults. Patients with mixed dyslipidemia who also have a lower concentration of apoB (apolipoprotein B) than predicted by total cholesterol levels may be suspected of having DBL. However, polyacrylamide gradient electrophoresis, lipoprotein ultracentrifugation (the traditional Fredrickson approach), or—more recently—the use of apoB algorithms as a screening tool are the best methods for diagnosing DBL (2–5). Physical characteristics such as palmar xanthomas and tuberous or tuberoeruptive xanthomas are symptomatic of DBL.Significantly, new research indicates that the prevalence of DBL may be higher than previously believed attaining a frequency in US adults of 1.7% to 2.0% (6). DBL patients have a higher risk of cardiovascular disease because the leftover

particles can enter the artery's intima-media region. In particular, prior research has indicated a significant risk of peripheral vascular disease (PVD) in these patients, ranging from 7% to 31% based on the DBL classification and study design (7–13). But the data in these research was retrospective, and the majority of the cohorts only contain a small number of people.Interestingly, the risk of PVD was 11 times higher in ρ2Є2 persons than in the non-ρ2Є2 group in a recent retrospective analysis that included 524 individuals who met the Fredrickson criteria (14). Only one prior study (n = 62) evaluated the PVD risk between patients with DBL and normolipidemic controls (n = 364); the results showed an odds ratio of 19.42. After the Bonferroni correction, the P value did not, however, approach the significant level (11). Additionally, no investigation examined the risk of peripheral vein disease (PVD) and coronary artery disease in people with familial hypercholesterolemia (FH), two diseases linked to a high cardiovascular risk (15).

Notably, DBL is still not well understood by physicians and is frequently misdiagnosed and undertreated, even though it carries a substantial risk of cardiovascular disease (16, 17). The current study aimed to assess the incidence of PVD, major adverse cardiovascular events (MACE), and atherosclerotic cardiovascular disease (ASCVD) in a cohort of patients with DBL vs normolipidemic CTLs and patients with FH.

SUPPLIES AND PROCEDURES

Examine the Population and Data Gathering

The Montreal Clinical Research Institute (IRCM) lipid clinic was the site of this study, which involved 1481 normolipidemic CTLs, 725 patients with FH, and 221 patients with DBL. During each patient's initial visit to the lipid clinic, knowledgeable doctors and nurses gathered the patient's medical history and baseline parameters.

Medical records were reviewed in order to gather this data for research. The observation period for this investigation was from birth until the final possible medical visit due to the hereditary basis of DBL and FH. Written informed consent from each patient enrolled in the research database was approved by the IRCM ethical institutional review board for human subjects research. The Declaration of Helsinki was followed in the conduct of the study.

FH group

Every FH patient included in this investigation had a molecular diagnosis; comprehensive procedures for this group have been previously published (18). Prior to baseline (untreated lipid profile), patients enrolled in primary cardiovascular prevention completed a 4-week washout of cholesterol-lowering medication. Patients who had a history of cardiovascular disease at baseline were assigned to the lipid profile with the highest LDL-C value at follow-up.

DBL group

The Fredrickson criteria (TG >1.5 mmol/L + very low-density lipoprotein cholesterol [VLDL-C]/TG >0.30 [ratio in mg/dL] [or >0.69 in mmol/L]) together with the APOE Є2Є2 status were used to diagnose DBL. A 4-week fibrate washout was administered to each patient prior to the baseline visit. A 4-week statin medication washout was also carried out for individuals receiving primary cardiovascular prevention.

Cohort CTL

The following criteria were met in order for the normolipidemic CTLs to be included: a maximal LDL-C concentration of ≤4.0 mmol/L, age ≥18 years at baseline, and baseline LDL-C and TG concentrations of <3.5 mmol/L and <2.0 mmol/L, respectively, without having had stain or fibrate treatment. The exclusion criteria included having Є2Є2, having a pathogenic or FH-causing mutation in the lipoprotein lipase (LPL) gene, having a broad beta band on electrophoresis, or having xanthomas.

Cardiovascular Outcomes

The main composite endpoint was ASCVD, which included the following events: myocardial infarction, peripheral revascularization (peripheral angioplasty or peripheral arterial bypass surgery), hospital admission for unstable angina, clinically verified claudication (by means of the ankle brachial index or Doppler), stroke, and cardiovascular death. MACE and PVD were the secondary composite endpoints. Whereas PVD comprised clinically verified claudication and lower-extremity revascularization (peripheral angioplasty and peripheral arterial surgery), MACE included myocardial infarction, stroke, coronary revascularization, hospital admission for unstable angina, and cardiovascular death. A doctor from the research team evaluated each cardiovascular event separately based on information from clinical consultations, ER visits, hospital stays, and test results.

Analyses Biochemical

All participants had a 12-hour overnight fast before having blood collected for biochemical analyses at baseline. The IRCM Lipid Laboratory used ultracentrifugation (beta-quantification) to measure blood lipid values, including measured LDL-C. Paquette et al. (14) provide the procedures for lipoprotein ultracentrifugation and the apoE phenotype or APOE genotype.

Analytical Statistics

For normally distributed continuous variables, baseline characteristics were defined as mean±SD and median (Q1-Q3). for categorical variables and frequency (%) for continuous variables with a skewed distribution. P values for categorical variables were determined using the chi-squared test. The

analysis of variance was used to examine group differences for continuous variables, and either the nonparametric Kruskall-Wallis test or the Tukey test came next. A two-tailed analysis was conducted, with significance being determined as P <.05, unless Table 3 specifies a different P value following Bonferroni adjustment.For the statistical studies, IBM SPSS Statistics 26 (IBM Corp., Armonk, NY) was utilized. The Kaplan-Meier technique was used to estimate the event-free survival, and the log-rank test was used to assess group differences. To evaluate the relationship between the lipid state and cardiovascular events, adjusted for age and sex (model 2) and age, sex, hypertension, diabetes, smoking, HDL-C, and LDL-C (model 3), risk ratios (HRs) and 95% confidence intervals (CIs) were produced using Cox proportional hazards regression analysis. There was no impute applied to make up for the absent data.

Baseline characteristics of the results

Table 1 displays the patients' initial lipid condition-related features. In all, 1481 CTLs, 221 DBL patients, and 725 FH patients were involved in this investigation. There were substantial differences in every analyzed variable between the groups. While the percentages of diabetes and hypertension were highest in DBL and lowest in CTL, the proportion of men and age at referral was highest in DBL (50 years), followed by CTL (41 years), and then FH (37 years). There was an equal amount of smokers in DBL and CTL, but far less so in FH. DBL's body mass index was noticeably higher than those of CTL and FH.

collectives. In terms of the lipid profile, the highest levels were found in TGs and VLDL-C, while the lowest levels were found in HDL-C, which was followed by FH and then CTL in DBL. Total cholesterol, non-HDL-C, and apoB concentrations were highest in the FH group, followed by DBL and CTL. Compared to the DBL and CTL groups, the FH group had significantly greater LDL-C.Although there were no xanthomas in the CTL group, the DBL group had a higher prevalence of DBL-related xanthomas (tuberous or tuberoeruptive, eruptive, and striated palmar xanthomas) than the FH group (P <.0001). Additionally, the prevalence of tendinous xanthomas was 49% in FH compared to 7% in DBL.

Analysis of Survival

Table 2 shows the frequency of each cardiovascular endpoint for each group. Table 3 shows that when the Cox regression was adjusted for age, sex, hypertension, diabetes, smoking, HDL-C, and LDL-C (P<.003), there was an overall excess risk of MACE (HR 2.69, 95% CI 1.50-4.80), PVD (HR 13.58, 95% CI 4.76-38.75), and ASCVD (HR 3.55, 95% CI 2.17-5.83) among patients with DBL vs normolipidemic CTLs. Between the two groups, there was no statistically significant difference in the incidence of stroke (P=.31).Compared to the FH group, PVD (HR 3.89, 95% CI 1.20-12.55, P=.02) was seen in the DBL group (Table 4). When contrasting FH with FH was linked to a significantly higher incidence of myocardial infarction, MACE, and ASCVD (P<.001) in normolipidemic CTLs (Table 5).

Fig. 1 presents the group's Kaplan–Meier event-free survival analysis for the incidence of ASCVD, MACE, and PVD. According to the Kaplan-Meier analyses, there was a significant difference (P≤.001) in the probability of event-free survival for each outcome across the three groups. When compared to patients with DBL (42%±7% and 53% ±8%) and CTLs, the FH group had the lowest event-free survival for ASCVD (35%±6%) and MACE (35%±6%) 79.9±9% and 81.1±9%, in that order. PVD-free survival was estimated by Kaplan-Meier to be 74% ±4% in patients with DBL, 86% ±3% in those with FH, and 99% ±1% in the CTL group.

DISCUSSION

Although a genetic abnormality and a substantial cardiovascular risk are shared by both FH and DBL illnesses, their clinical presentation and characteristics are very distinct. FH is an autosomal codominant condition that is usually linked to hypercholesterolemia and early-life cardiovascular disease in the family. Since DBL is primarily recessively inherited, there isn't a significant history of atherosclerosis in the family. Patients with DBL have a mixed hyperlipidemia (high total cholesterol and TG concentrations) and more commonly have cutaneous xanthomas (tuberous, tuberoeruptive, striated palmar, and eruptive). In contrast, patients with FH have extremely high LDL-C concentrations (>95th percentile for age and sex) and frequently have tendinous xanthomas.With an observation length of 11 114 person-years (mean of 60 years), this study represents the largest published cohort of patients with DBL who have been diagnosed using a strict diagnosis of DBL (gold standard Fredrickson criteria + Є2Є2). This is also the first to describe the prevalence of cardiovascular disease in DBL patients relative to FH and normolipidemic CTL patients.

Two important conclusions came from this investigation. First off, compared to normolipidemic CTLs, patients with DBL had a roughly three-fold increased risk of incident ASCVD and MACE as well as a >13-fold increased risk of incident PVD. Second, compared to patients with FH, patients with DBL have a PVD risk that is approximately four times higher.

Our findings supported earlier research, which was predicated on smaller cohorts, that indicated this demographic carries a significant risk of PVD. In fact, the unadjusted and adjusted HR for PVD in the DBL group in our study varied from 19.77 to 13.58 when compared to the CTL group. These findings are comparable to those of Tremblay et al., who found an adjusted odds ratio of 19.42 (11).We found that there is a roughly 10-year difference in the onset of events between FH

and DBL when examining the Kaplan-Meier curves for the probability of ASCVD-free survival. This difference is mostly caused by coronary events. This finding may be explained by the fact that, in genetically confirmed FH, the remnant accumulation starts later in life (between the third and fifth decade), coinciding with the onset of metabolic disorders like insulin resistance. In DBL, on the other hand, the remnant accumulation starts later in life.

Crucially, even while dyslipidemia manifests later in DBL patients than in FH patients, the disease's elevated risk is amply demonstrated by the faster atherosclerosis that develops in DBL patients.This study offers strong evidence in favor of the necessity of educating medical professionals about DBL diagnosis, treatment, and the rapid and serious complications that can arise from the condition.

The significant increase in residual particles found in DBL is the primary mechanism linking the condition to a higher risk of PVD. In fact, a number of extensive prospective investigations found a correlation between PVD in the general population and remnant particle or cholesterol content (1, 19–21). Because of their tiny size, cholesterol-enriched VLDL particles can cross the endothelium barrier.

They are phagocytized by macrophages, which results in the accumulation of foam cells and the formation of atherosclerosis. Low grade inflammation may also be linked to the hydrolysis of TGs from VLDL remains, which would worsen the atherogenic process (22–24). It is also unclear, nevertheless, how leftover particles might be more atherogenic in bigger arterial beds—such the lower limb arteries—than in smaller arteries, like the coronary arteries.

The first steps in treating DBL are changing one's lifestyle and controlling secondary risk factors well. These measures can include quitting smoking, losing weight, or managing blood pressure. Clinical therapies that modify insulin resistance frequently have a significant impact on the lipid profile of individuals with DBL since insulin resistance is frequently the secondary triggering factor in many DBL patients. To attain the best possible control, medication comprising statins and fibrates may also be started; a referral to a specialized lipid clinic is advised (25). Significantly, it has been demonstrated that the DBL phenotype is variable, with a higher severity in persons with genetic confirmation (Є2Є2 genotype) than in those with a diagnosis based solely on the VLDL-C/TG ratio (14).Therefore, more drastic lifestyle modifications and treatment would be beneficial for those with a more severe version of the disease. A recent study examined the effects of evolocumab, an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9), in a small group of three DBL patients. According to this investigation, this treatment approach was successful in lowering the concentrations of VLDL, remnants, intermediate-density lipoprotein, and LDL particles in addition to VLDL-C (26).

There are several advantages and disadvantages to the current investigation. One of the main advantages is that the three patient groups originated from the same lipid clinic, and their baseline visit took place in a comparable time frame. Additionally, a substantial number of normolipidemic CTLs and well-characterized DBL patients who were diagnosed under rigorous criteria were included in this study. One study disadvantage is that patients with DBL who had genetic determinants other than the Є2Є2 genotype, like uncommon dominant variations in APOE, were not included in our cohort. Whether the phenotypes of these two patient groups are comparable in terms of severity is still unknown.Moreover, the CTL participants might not be entirely representative of the general population because they were chosen through a lipid clinic. Lastly, because the majority of the study population was European, further research is required to confirm the findings among other ethnic groups.

CONCLUSION

In summary, compared to normolipidemic CTLs, patients with DBL have a risk of PVD that is >13 times higher and an increased risk of ASCVD that is >3 times higher.

Moreover, patients with DBL had a roughly 4-fold increased risk of PVD compared to those with FH. These findings highlight how crucial it is to screen DBL patients thoroughly in order to enhance their clinical treatment and stop atherosclerosis from developing. Subsequent research ought to assess the prevalence of peripheral and coronary endpoints in DBL individuals in contrast to those with other types of mixed dyslipidemia.

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