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Research Article

Palmar Striated Xanthomas in Clinical Practice

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Abstract

Context: Palmar striated xanthomas (PSX) are macular subcutaneous lesions conferring a yellow-to-orange coloration of palmar and finger creases that characterize dysbetalipoproteinemia, a disease associated with sustained plasma accumulation of triglyceride-rich lipoprotein remnants. Although remnants accumulation may occur in any condition interfering with triglyceride-rich lipoprotein hydrolysis or clearance, the presence of PSX has not been systematically assessed across the spectrum of lipid disorders potentially associated with sustained or recurrent remnants accumulation.

Objective: The aim of this study was to assess the occurrence of (PSX) in a wide spectrum of lipid disorders ranging from very severe hypercholesterolemia (homozygous familial hypercholesterolemia) to very severe hypertriglyceridemia (chylomicronemia).

Methods: This study involved 3382 dyslipidemic White adult patients (1856 men and 1526 women) seen at the Chicoutimi Hospital Lipid Clinic (Quebec, Canada), covering a wide range of lipid disorders, from severe hypertriglyceridemia to severe hypercholesterolemia. Categorical variables were compared using the Pearson χ^2 statistic, whereas univariate analysis of variance or nonparametric Kruskal-Wallis was used for continuous variables.

Results: A total of 5.1% (173/3382) of the studied patients presented PSX, a majority of them (67.1%) being women. PSX were observed in 18.8% of patients with dysbetalipoproteinemia and also among 14.1% of hypertriglyceridemic patients with partial lipoprotein lipase deficiency, 3.7% of patients with chylomicronemia, and in all those with homozygous familial hypercholesterolemia. Overall, 10.7% of patients with PSX did not meet dysbetalipoproteinemia diagnosis criteria.

Conclusion: According to our study, the PSX prevalence estimate among patients without dysbetalipoproteinemia would be around 10% and they could be observed in a wide spectrum of lipid disorders associated with recurrent or sustained remnant lipoprotein accumulation.

Key Words: apolipoprotein E, dyslipidemia diagnosis, palmar striated xanthomas, remnant lipoproteins, dysbetalipoproteinemia

Abbreviations: Apo, apolipoprotein; FCS, familial chylomicronemia syndrome; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; HL, hepatic lipase; HoFH, homozygous familial hypercholesterolemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; MCS, multifactorial chylomicronemia; PSX, palmar striated xanthomas; RFLP, restriction fragment length polymorphism; T2D, type 2 diabetes; TGs, triglycerides; VLDL, very-low-density lipoprotein.

Palmar striated xanthomas (PSX) are subcutaneous lesions characterized by a yellow to brownish coloration of palmar and finger creases (Fig. 1) [1, 2]. Their physiopathology is not well described in the current literature. Extrapolating from the histologic findings related to other kinds of xanthomas, it can be hypothesized that an increased permeability of dermal capillaries to lipids is required to initiate the development of xanthomas. If triglyceride (TG)-rich lipoprotein remnants (intermediate-density lipoprotein, IDL) accumulate, the generated inflammatory response can lead to the formation of foam cells and the recruitment of inflammatory cells to form PSX [3-6]. A significant proportion of untreated patients with dysbetalipoproteinemia (formerly known as type III) present with PSX [7, 8], a clinical sign often referenced as pathognomonic of this disorder. Dysbetalipoproteinemia, a disease characterized by accumulation of remnants (IDL) in the plasma, is a highly atherogenic hyperlipidemia associated with increased peripheral and coronary artery disease risks [9, 10]. This remnant disease is most often associated with an apolipoprotein (Apo) E dysfunction and requires the presence of factors leading to an overproduction or a decrease of clearance of remnants, such as obesity, type 2 diabetes (T2D), or other factors. The genetic basis of ApoE abnormality is well documented and is most often (but not always) associated with polymorphisms in the *APOE* gene. There are 3 main gene variants, *APOE2*, *APOE3*, and *APOE4*, coding for corresponding ApoE isoforms; the most frequent in all populations is ApoE3. Compared to ApoE3, ApoE2 differs by one amino acid at position 158. This modification causes ApoE2 difficulties in binding to the low-density lipoprotein receptor (LDLR), LDLR-related protein, and heparan sulphate proteoglycans, which may ultimately lead to remnant accumulation [11, 12].

However, remnant accumulation is not restricted to dysbetalipoproteinemia. It may also occur in any condition recurrently or sustainably interfering with TG-rich lipoprotein hydrolysis or remnant clearance, including postprandial dyslipidemia and chylomicronemia, partial

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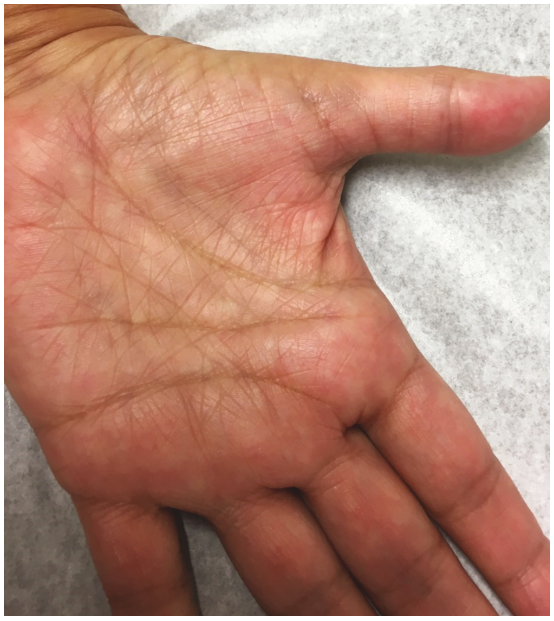

Figure 1. Palmar striated xanthomas.

lipoprotein lipase (LPL) deficiency, or severe refractory familial hypercholesterolemia (FH), including homozygous FH (HoFH). The aim of this study was to assess the occurrence of PSX in patients with different lipid-lipoprotein disorders potentially associated with remnant accumulation.

Material and Methods

Participants and Clinical Data

This study included 3382 adult White individuals seen at the Chicoutimi Hospital Lipid Clinic. This regional reference clinic has been in service for 30 years and follows some 6000 adult and pediatric patients [13]. All individuals agreed to participate in studies on genetic determinants of T2D or coronary artery disease. The physical exam, including the assessment of the presence of PSX, was performed by 2 experienced lipidologists (including DG) at this specialized clinic before the start of any lipid-lowering therapy for all drug-naive patients. Dysbetalipoproteinemia diagnosis was confirmed by the presence of 3 or more of the following criteria: TGs greater than or equal to 1.7 mmol/L; TGs/ApoB less than 10 mmol/g; total cholesterol/ApoB greater than or equal to 6.2 mmol/g; very-low-density lipoprotein (VLDL) cholesterol/TGs greater than or equal to 0.5; APOE2/E2 genotype; as well as the presence of PSX or tuberous xanthomas [9] (Table 1). Since the ApoE2 genotype is not the only possible cause of an ApoE dysfunction, some patients will carry only one apoE2 allele and, for some, none at all. Conversely, not all ApoE2 homozygous patients with a metabolic disorder will have dysbetalipoproteinemia. Diagnosis criteria were therefore used for all patients, even when the ApoE genotype was available.

T2D was defined using Diabetes Canada clinical practice guidelines [14]. Waist girth was measured according to the procedures of the Airlie conference [15]. Obesity was defined as a body mass index greater than or equal to 30. Metabolic syndrome was diagnosed by the presence of 3 or more of the following: waist circumference greater than 88 cm for women or greater than 102 cm for men; TGs greater than 1.7 mmol/L; high-density lipoprotein (HDL) cholesterol less than 1.3 mmol/L for women or less than 1.0 mmol/L for men; high blood pressure defined as greater than or equal to 130/85 (or on treatment for blood pressure) or blood glucose greater than or equal to 5.6 mmol/L [16]. Partial LPL deficiency was confirmed using genotyping. The simplified Canadian definition of FH and molecular diagnosis were used to confirm the FH diagnosis [17], whereas multifactorial (MCS) and familial chylomicronemia syndrome (FCS) diagnoses were based on molecular analyses and diagnosis scoring systems [18, 19]. Although other clinical phenotypes are potential modulators of remnants accumulation, this study was restricted to the most prevalent and significant disorders in lipid clinic practice. Drug-naive lipid profiles were available for 2837 (84%) patients, while other patients received either statins (74.3%), fibrates (26.3%), ezetimibe (4.8%), resins (4.8%), or niacin (2.7%). Of these patients, 12.2% received more than one class of medications. Individuals gave their informed consent to participate in this study and were assigned a code that systematically deidentifies all clinical data [20].

Table 1. Diagnostic criteria for dysbetalipoproteinemia used in this study

Presence of at least 3 of the following criteria
TGs ≥ 1.7 mmol/L
TGs/ApoB < 10 mmol/g
TC/ApoB ≥ 6.2 mmol/g[a]
VLDL-C/TGs ≥ 0.5
ApoE2/E2 genotype
Presence of palmar striated xanthomas or tuberous xanthomas

Abbreviations: ApoB, apolipoprotein B-100 measured on delipidated plasma; ApoE2/E2, homozygous for allele *E2*; TC, total cholesterol; TGs, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.
[a]In mg/dL, TC and TG levels are similar.

This project was approved by the Chicoutimi Hospital Ethics Committee and IRB Services (now Advarra). Written informed consent was obtained from each patient. The work was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki).

Biochemical Analyses

Blood samples were obtained after a 12-hour overnight fast from the antecubital vein into vacutainer tubes containing EDTA. Cholesterol, TGs, and glucose levels were measured by enzymatic assays on a CX7Analyser (Beckman) [21]. Total cholesterol was determined in serum and HDL after precipitation of VLDL and LDL (d > 1.006 g/mL) in the infranatant with heparin and manganese chloride ($MnCl_2$). Serum LDL cholesterol levels were estimated using the Friedewald formula [22] unless the TG level was greater than 4.5 mmol/L, in which case a direct measurement was used [23]. For a subsample of 1118 patients, VLDL particles (d < 1.006 g/mL) were isolated by ultracentrifugation, whereas the HDL subfraction was obtained after precipitation of LDL with dextran sulfate and $MnCl_2$. Cholesterol and TG levels were measured in each subfractions [24]. ApoB levels were determined using nephelometry, and nonesterified fatty acid levels were determined using an enzymatic assay. Serum glycerol concentrations were measured with an analyzer Technicon RA-500 (Bayer Corp), and enzymatic reagents were obtained from Randox Laboratories. The remnant cholesterol, defined as the cholesterol content of TG-rich remnant lipoproteins,

was estimated by total cholesterol – (LDL cholesterol + HDL cholesterol) [25].

Genotyping

ApoE genotyping was performed using a restriction fragment length polymorphism (RFLP) analysis with the HhaI restriction enzyme. After cleavage of amplified sequences in specific regions, the DNA fragments were separated by electrophoresis on a polyacrylamide gel [26]. The presence of FCS and FH-causing mutations in the LPL and LDLR genes, respectively, was identified using a mismatch polymerase chain reaction–restriction fragment length polymorphism as previously described [27-31].

Statistical Analysis

Categorical variables were compared using the Pearson χ^2 statistic, whereas group differences for continuous variables were examined with a univariate analysis of variance or nonparametric Kruskal-Wallis tests followed by Game-Howell tests when the homogeneity of the variance was not respected. Statistical significance level was set at P less than .05. All statistical analyses were performed with the SPSS package (release 25.0, SPSS).

Results

Table 2 shows that 5.1% (173/3382) of the study participants presented with PSX, most of them (67.1%) being women. Body mass index and mean fasting glucose levels were significantly higher in patients with PSX ($P = .001$). These differences remained statistically significant even among individuals without diabetes ($P = .017$ and .011). A total of 18.0% of patients with PSX were homozygote for APOE2, whereas 44.8% were APOE2 ($P < .001$).

The results presented in Table 3 illustrate that the presence of PSX is associated with higher plasma levels of total cholesterol ($P < .001$), TGs ($P < .001$), and Apo B ($P = .073$), but significantly lower levels of LDL ($P = .001$). Patients with PSX had significantly higher TG levels in all lipoprotein fractions ($P \leq .007$). The occurrence of PSX was also associated with higher levels of remnant cholesterol, free glycerol, and nonesterified fatty acid and with higher values of VLDL cholesterol/VLDL-TGs, VLDL-cholesterol/TGs, and TG/ApoB ratios ($P \leq .001$). Similar results were observed when analyses were conducted in women and men separately (data not shown).

The occurrence of PSX in relation to the clinical diagnosis is shown in Table 4. All genetically confirmed HoFH patients in this study presented with PSX. A statistically significant proportion of patients with dysbetalipoproteinemia (18.8%) and genetically confirmed partial LPL deficiency (14.1%) also presented with PSX. Between 5% and 10% of patients diagnosed with obesity, T2D, hypothyroidism, or a full metabolic syndrome had PSX. Some patients with refractory heterozygous FH or with MCS also presented with PSX. These diagnoses are not mutually exclusive; patients can have more than one diagnosis. Combinations of diagnoses involving dysbetalipoproteinemia are those associated with the highest prevalence of PSX: 29.1% among patients with dysbetalipoproteinemia and type 2 diabetes, and 26.1% among those with dysbetalipoproteinemia and obesity. Interestingly, the prevalence of PSX reached 18.8% in patients with T2D and hypothyroidism. All other combinations provided similar results to those shown in Table 4. We also found that 12.8% (5/39) of hypertriglyceridemic patients with myotonic dystrophy presented with PSX, a feature that has already been reported [32]. Highly similar results were observed among the whole sample and drug-naive patients (data not shown).

Among the 150 patients with dysbetalipoproteinemia and PSX, 20.7% were found to be homozygous for ApoE2, whereas the rate of PSX was 27.2% among the dysbetalipoproteinemia-ApoE2/E2 patients and 20.3% among the dysbetalipoproteinemia non–ApoE2/E2 homozygous individuals ($P = .1$). Finally, overall, 10.7% of patients with PSX in this study did not meet a sufficient number of criteria to have a diagnosis of dysbetalipoproteinemia (data not shown).

Discussion

A total of 5.1% of patients included in this study had PSX, including those with dysbetalipoproteinemia, HoFH, and partial LPL deficiency. The presence of PSX was also observed among 5% to 10% of patients with obesity, T2D, hypothyroidism, or metabolic syndrome and in some patients with heterozygous FH or severe hypertriglyceridemia (chylomicronemia). PSX were observed despite the absence

Table 2. Patients' characteristics according to presence of palmar striated xanthomas

	Without PSX n = 3209	With PSX n = 173	*P*
Age, y	47.7 ± 12.4	48.6 ± 13.0	NS
Female, n (%)	1410 (43.9)	116 (67.1)	< .001
Menopausal[b], n (%)	724 (56.6)	69 (64.5)	NS
Waist[c], cm	91.6 ± 13.5	91.6 ± 13.7	NS
BMI[d]	27.5 ± 4.8	28.7 ± 5.2	.001
Fasting glucose[a,e]	5.2 (4.8-5.7)	5.4 (5.0-6.0)	.001
ApoE2[f], n (%)	486 (25.6)	77 (44.8)	< .001
ApoE2/E2[f] n (%)	94 (5.0)	31 (18%)	< .001

Data are mean ± SD unless otherwise specified. NS = P greater than .10.
Abbreviations: ApoE2, presence of one apolipoprotein E2 allele; ApoE2/E2, homozygous for allele E2; BMI, body mass index; NS, not significant; PSX, palmar striated xanthomas.
[a]Median (interquartile range). Among a subsample of (n): [b] = 1387; [c] = 3055; [d] = 3321; [e] = 3239; [f] = 2068.

Table 3. Lipid profile according to presence of palmar striated xanthomas among patients without lipid-lowering medication

	Without PSX n = 2678	With PSX n = 159	*P*
Total C, mmol/L	7.67 ± 2.26	8.93 ± 4.19	< .001
HDL-C[b], mmol/L	1.09 ± 0.37	1.07 ± 0.43	NS
LDL-C[c], mmol/L	5.06 ± 1.95	4.22 ± 2.92	.001
TGs[a,d], mmol/L	2.20 (1.40-4.10)	4.8 (2.3-8.8)	< .001
Non–HDL-C[a,e]	6.20 (5.20-7.40)	6.50 (5.50-8.40)	.009
ApoB[f], g/L	1.28 ± 0.36	1.35 ± 0.47	.073
NEFA[a,g]	0.54 (0.40-0.71)	0.59 (0.49-0.77)	.001
Glycerol[a,h]	0.07 (0.05-0.10)	0.08 (0.06-0.12)	<.001
Remnant C[a,i]	0.90 (0.60-1.40)	1.70 (0.84-4.07)	<.001
TC/ApoBB[a,f]	5.73 (4.97-6.89)	5.70 (5.05-7.66)	NS
TGs/ApoB[a,j]	1.85 (1.15-3.60)	3.61 (1.86-7.29)	<.001
non-HDL/ApoB[a,k]	4.81 (4.18-5.78)	4.90 (4.14-6.33)	NS
Lipid profile from ultracentrifugation n (1118)			
	n = 970	**n = 148**	
VLDL-TGs[a], mmol/L	1.72 (0.95-3.09)	2.71 (1.14-4.18)	<.001
VLDL-C[a], mmol/L	1.52 ± 1.75	2.38 ± 2.35	<.001
LDL-TGs[a], mmol/L	0.42 (0.32-0.55)	0.48 (0.34-0.64)	.007
LDL-C, mmol/L	3.73 ± 1.62	3.71 ± 2.53	NS
HDL-TG[a], mmol/L	0.29 (0.24-0.38)	0.36 (0.27-0.45)	<.001
HDL-C, mmol/L	0.95 ± 0.32	0.97 ± 0.39	NS
VLDL-C/VLDL-TGs[a]	0.59 (0.50-0.71)	0.68 (0.53-0.87)	<.001
VLDL-C/TGs[a]	0.39 (0.33-0.45)	0.44 (0.36-0.57)	<.001

Data are mean ± SD unless otherwise specified. NS = *P* greater than .10
Abbreviations: ApoB, apolipoprotein B-100 measured on delipidated plasma; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NEFA, nonesterified fatty acid; NS, not significant; PSX, palmar striated xanthomas; TGs, triglycerides; VLDL, very-low-density-lipoprotein.
[a]Median (interquartile range). Among a subsample of (n): [b] = 2724; [c] = 2554; [d] = 2835; [e] = 2724; [f] = 1976; [g] = 1487; [h] = 1637; [i] = 2472; [j] = 1974; [k] = 1879.

Table 4. Presence of palmar striated xanthomas according to clinical diagnosis[a]

	Total No.	Without PSX n (%)	With PSX n (%)
Obesity	860	795 (92.4)	65 (7.6)
Type 2 diabetes	475	436 (91.8)	39 (8.2)
Metabolic syndrome	1467	1366 (93.1)	101 (6.9)
Partial LPL deficiency	348	299 (85.9)	49 (14.1)
Dysbetalipoproteinemia	799	649 (81.2)	150 (18.8)
Chylomicronemia (FCS/MCS)	27	26 (96.3)	1 (3.7)
Homozygous FH	8	0 (0.0)	8 (100.0)
Heterozygous FH	1185	1155 (97.5)	30 (2.5)
Hypothyroidism	290	262 (90.3)	28 (9.7)

Abbreviations: FCS, familial chylomicronemia syndrome; FH, familial hypercholesterolemia; LPL, lipoprotein lipase; MCS, multifactorial chylomicronemia; PSX, palmar striated xanthomas.
[a]Diagnoses are not mutually exclusive; patients can have more than one diagnosis.

of dysbetalipoproteinemia in more than 10% of patients. Various criteria and algorithms were used to diagnose dysbetalipoproteinemia [33-35]. The use of the Sniderman [33] or the Frederickson algorithm criteria [36] in the present study did not change the observation. PSX were seen in conditions other than dysbetalipoproteinemia, including in a variety of lipid disorders potentially associated with remnant (IDL) accumulation. It is noteworthy that, while age is known as a risk factor of dysbetalipoproteinemia and a well-known covariable of various potential modulators of remnant production or clearance, there is no statistically significant difference in age according to the presence of PSX in the present study. Moreover, to the best of our knowledges, there are also no data in the literature about the relation between PSX and patient age. Finally, not all patients who fulfill dysbetalipoproteinemia diagnosis criteria have PSX. However, the proportion of dysbetalipoproteinemia patients with PSX in this study is lower than that observed in previous studies, which reported a prevalence between 20% and 72% [37-39].

PSX are macular yellowish colorations of the palmar and finger creases that can easily be missed. The pathophysiology underlying the occurrence of this finding is not fully understood and poorly described in the literature. Walton et al [4] proposed that the palmar distribution of striated xanthomas could be related to minor traumas secondary to the pressure loading to which they are exposed. These repeated traumas, associated with remnant-induced inflammation, would ultimately lead to an increase in vascular endothelial permeability and leakage of lipids through the vascular endothelial wall [4, 12]). The accumulation of intracellular and extracellular lipids associated with the inflammation would ultimately lead to the progression of the lesion and formation of PSX. Considering that the cholesterol content of TG-rich lipoprotein is behind the inflammatory response

associated with dyslipidemia and that dysbetalipoproteinemia is one of the best models of remnant accumulation (mostly IDL), our results are consistent with the fact that remnant concentrations might predispose individuals to PSX.

The presence of PSX has been previously reported in severe FH [40-44] as well as in other conditions, such as primary biliary cirrhosis [45-47], a disease associated with hepatic lipase (HL) activity reduction. HL deficiency interferes with remnant (IDL) hydrolysis and LDL production. In the later stage, primary biliary cirrhosis can be associated with the accumulation of lipoprotein-X, a phospholipid-rich and TG-poor lipoprotein [48]. The contribution of lipoprotein-X to the development of PSX is not documented. Patients with myotonic dystrophy can also exhibit PSX, when the linkage disequilibrium is with APOE2 instead of APOE4 [32]. Finally, PSX are observed in patients with multiple myeloma [49, 50], a disease associated with interference in the catabolism of lipoprotein by the paraprotein [51]. Except for myotonic dystrophy, these disorders were not represented in our study. However, taken together, these observations suggest that PSX is a clinical sign reflecting the importance of remnant metabolism in health and disease. Considering that remnant cholesterol is an important correlate of cardiovascular outcomes, independently of several other risk factors and, in some conditions, more important than LDL and HDL cholesterol levels [52, 53], this suggests that PSX could have an important implication in individual risk evaluation. Clinicians would benefit from adding this quite simple assessment during physical exams. With the still increasing obesity pandemic, PSX could be far more prevalent than initially thought.

In the study population, the prevalence of APOE2 in patients with PSX was approximatively 50%, among which 20% were homozygotes. In the Blom cohort, genotypes other than APOE2 explained 51% of dysbetalipoproteinemia cases [39]. Although it is well documented that APOE2 homozygocity confers an important susceptibility to ApoE dysfunction [8], our results concur with the view that other factors can contribute to remnant accumulation and to the pathophysiology leading to the formation of PSX as proposed by Murase et al [54].

The results of this study suggest that various elements characterizing a large spectrum of lipid lipoprotein disorders may contribute to remnant accumulation and to the expression of PSX in the absence of dysbetalipoproteinemia. Remnants accumulate secondarily to an increase of TG-rich lipoprotein production or a decrease of clearance (Fig. 2). Several lipid lipoprotein disorders can therefore lead to sustained or recurrent remnant accumulation, including partial LPL deficiency (genetic or functional), severe FH, including HoFH, HL deficiency, HDL-related disorders, and multifactorial hypertriglyceridemia [10]. Clinical phenotypes, such as obesity, high blood glucose, diabetes, metabolic syndrome, and hypothyroidism, are potential modulators of remnant production or clearance. In patients with chylomicronemia (sustained TG concentration > 10 mmol/L), the ability to accumulate remnants depends on the underlying cause and the residual LPL activity available. Patients with complete LPL deficiency (FCS) are physiologically unable to produce remnants. Thus, the presence of PSX in a patient with chylomicronemia suggests the diagnosis of MCS, which is more frequent than FCS and is associated with some residual LPL activity.

The main strengths of our study are the large spectrum and the diversity of lipid lipoprotein disorders studied, the standardized clinical and biochemical phenotyping, and the availability of genetic data. Our does study have limitations,

Figure 2. Remnants and other lipoproteins accumulation according to type of lipid disorder. CM, chylomicron; CM-re, chylomicron remnants; FCHL, familial combined hyperlipidemia; FCS, familial chylomicronemia syndrome; FH, familial hypercholesterolemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MCS, multifactorial chylomicronemia syndrome; VLDL, very-low-density lipoprotein.

however. First, it was performed in a sample issued from a relatively homogeneous White population. Results must therefore be replicated in larger and more diversified samples. Besides being retrospective, the study was not designed to specifically detect the presence or absence of PSX, which may have led to misestimating their prevalence. However, because physicians who have performed physical exams are lipid specialists with great experience in the detection and documentation of PSX, we believe this potential bias was minimized. In addition, only 2 physicians performed all physical exams, which reduced the examiner effect. However, since PSX may regress and eventually disappear with several months of treatment, some could have been missed among patients on treatment. PSX were observed among 5.6% of drug-naive patients, while 2.6% of patients receiving lipid-lowering medication, or with an unknown treatment status, had PSX. Notwithstanding this difference in PSX prevalence, the combined analysis of lipid-lowering, drug-naïve, and nonnaive patients did not substantially affect the results obtained in the present study. It also would have been highly informative to have more data on PSX disappearance vs persistence as well as additional information on treatments and how adequately the clinical phenotypes included in the present study were controlled. The fact that cholesterol remnant levels were estimated and not directly measured is another limitation [55]. Finally, in our study, lipid lipoprotein levels were measured fasting. Considering that nonfasting lipid profile can add valuable information on remnant metabolism and the assessment of their transient accumulation, we did not consider the possible contribution of on-fasting lipid profiles to the occurrence of PSX. Fat meal challenges could have been added in this context [56], and such studies are ongoing. Further analyses, including receiver operating characteristics curves, are needed to specify the contribution of PSX and other variables to risk stratification.

Conclusion

Not all patients with PSX fulfill the criteria of dysbetalipoproteinemia diagnosis. According to our study, the PSX prevalence estimate among patients without dysbetalipoproteinemia would be around 10% and they could be observed in a large spectrum of lipid lipoprotein conditions associated with sustained remnant accumulation, which might explain their presence.

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Disclosures

The authors have nothing to disclose.

Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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