Influence of metabolic syndrome superposition on familial combined hyperlipoproteinemia cardiovascular complication rate

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Abstract

Introduction: Familial combined hyperlipoproteinemia (FCHL) is a very common and aggressive genetic mixed hyperlipoproteinemia, with many features similar to that of the metabolic syndrome (MS). We aimed to evaluate whether the presence of the MS per se could account for a significant part of the elevated cardiovascular disease (CVD) risk associated with FCHL.
Material and methods: A retrospective cross-sectional evaluation of MS features' influence on CVD prevalence in a large sample of adult Italian FCHL affected patients (64 familial clusters; 867 subjects) was carried out.
Results: Age is associated with early cardiovascular complications, both in men (OR 1.08, 95% CI: 1.05-1.11, $p < 0.0001$) and in women (OR 1.09, 95% CI: 1.04-1.13, $p = 0.0001$). No MS component appears to be related to cardiovascular complications in men, whilst only low plasma high-density lipoprotein cholesterol (HDL-C) shows such a relation in women. Among non-MS parameters, only low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) plasma levels are significantly associated with early cardiovascular complications in male FCHL patients (LDL-C: OR 2.24, 95% CI: 1.02-4.91, $p = 0.04$; Lp(a): OR 4.64, 95% CI: 1.85-11.62, $p = 0.001$), but not in women (LDL-C: OR 1.83, 95% CI 0.53-6.34, $p = 0.34$; Lp(a): OR 3.65, 95% CI: 0.89-14.97, $p = 0.07$).
Conclusions: Our data support the hypothesis that MS is not associated with a higher prevalence of cardiovascular complications in FCHL affected subjects, probably because of the strongest risk increase associated with the FCHL itself.

Key words: epidemiology, familial combined hyperlipoproteinemia, metabolic syndrome, prognosis, prevalence.

Introduction

Familial combined hyperlipoproteinemia (FCHL) is an inherited metabolic disorder characterized by intraindividual and/or intrafamilial variability of lipid phenotype, and by an increased risk of premature coronary heart disease (CHD) [1, 2]. The most frequently found laboratory abnormalities in FCHL are an increase of plasma triglycerides (TG) and/or cholesterol levels, and a high prevalence of small very-low-density lipoproteins (VLDLs) and/or low-density lipoproteins (LDLs), mainly related to an increase in plasma level of apolipoprotein B100 (apoB) [3]. Some patients can also present a decrease in HDL cholesterol plasma level, often inverse-

ly related to the TG plasma level [4]. Familial combined hyperlipoproteinemia is a risk factor for increased carotid artery intima-media thickness (IMT) [5] and arterial stiffness [6]. The parameters that mainly relate to IMT are the plasma apoB level and consequently the LDL particle size [7]. A worse prognostic factor appears to be the constant association of hypercholesterolemia with hypertriglyceridemia [8]. Hypertriglyceridemia per se seems in fact to be a significant predictor of cardiovascular disease in proportion to the baseline TG levels [9]. Familial combined hyperlipoproteinemia is one of the most common genetic hyperlipoproteinemias in the general population (estimated prevalence: 0.5-2.0%) [10], and the most frequent one in early acute myocardial infarction survivors (11.3%) [11] and overall in myocardial infarction survivors (up to 40%) [12].

The metabolic syndrome (MS) is also very frequent, ranging from 20% to 40% in the adult general population, and it is strongly linked to increased cardiovascular disease risk [13]. The broadening of diagnostic criteria for MS, as suggested by the third Adult Treatment Panel of the National Cholesterol Education Program [14], has caused significant overlapping with the FCHL diagnosis. Metabolic syndrome was identified in 65% of US FCHL patients compared with 19% in controls without FCHL and was associated with an odds ratio of 3.3 ($p < 0.0001$). The increased prevalence of the MS alone could account for at least a portion of the elevated CHD risk associated with FCHL [15].

The aim of our study was to investigate the influence of MS features on the prevalence of cardiovascular disease in a large sample of Italian FCHL affected patients.

Material and methods

We retrospectively sampled data on 868 patients (men: 636, women: 232) who were consecutively diagnosed with FCHL during the last 10 years of ambulatory practice in our lipid clinic and for each of whom a complete set of clinical and laboratory data were available. Inclusion criteria for FCHL subjects were:
- first visit to the lipid clinics of Bologna University or of Pavia University between December 1999 and December 2009;
- availability of at least a set of laboratory data (i.e. lipid profile, apolipoproteins B and AI, lipoprotein(a), fasting glycemia, fibrinogenemia, basal homocysteinemia) obtained in our laboratory before the beginning of any lipid-lowering therapy;
- diagnosis of FCHL (based on the criteria suggested by the Italian guidelines for FCHL detection and diagnosis [9]):
    – LDL-C > 160 mg/dl and/or TG > 200 mg/dl,

– apolipoprotein B100 > 125 mg/dl,
– documentation of intrafamilial phenotype variability at any given time or intraindividual phenotype shift over any time period,
– exclusion of other genetic causes of hyperlipoproteinemia,
– exclusion of secondary dyslipidemias, exclusion of iatrogenic interference with the phenotype shift,
– documentation of early CHD events and/or other premature and severe complications of atherosclerosis.

All laboratory parameters were obtained following standard procedures as fully described elsewhere [16].

Main anthropometric and laboratory data are reported in Table I.

Clinical cardiovascular events (defined as ICD-9 codes 410-414, 433-438, and 440) were considered premature if they occurred before the age of 55

Table I. Mean (SD) level of metabolic parameters of FCHL patients who visited the Lipid Clinic of the University of Bologna from June 2003 to June 2006

Parameter	Men (n = 636)		Women (n = 232)	
	Mean	SD	Mean	SD
Age [years]*	45.23	13.36	52.56	17.40
BMI [kg/m²]*	26.74	3.40	24.42	3.07
Waist circumference	102.38	12.61	91.72	6.44
SBP [mm Hg]	135.18	12.44	132.22	14.37
DBP [mm Hg]	92.15	4.37	90.08	3.88
TC [mg/dl]*	250.85	54.81	267.40	67.52
TG [mg/dl]*	251.55	161.62	219.04	154.33
LDL-C [mg/dl]*	158.49	49.27	172.43	60.14
HDL-C [mg/dl]*	44.01	10.75	52.01	14.29
APO-B [mg/dl]	130.36	35.67	129.90	37.10
APO-A1 [mg/dl]*	124.69	23.03	144.39	31.38
Lipoprotein(a) [mg/dl]*	23.84	19.04	47.38	35.04
Fibrinogen [mg/dl]*	282.59	90.27	314.41	53.22
Basal homocysteine [μmol/l]	10.19	3.86	10.12	9.0558
Fasting plasma glucose [mg/dl]*	95.32	14.16	102.15	52.78
TG/LDL-C*	1.75	1.367	1.36	1.02
TG/APOB*	2.11	1.59	1.40	0.70
Non HDL-C [mg/dl]	207.06	57.52	214.90	73.32

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, TC – total cholesterol, TG – triglycerides, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, ApoB – apolipoprotein B, ApoAI – apolipoprotein AI
*p < 0.05 between sexes

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years in men and before 65 years of age in women, whereas events reported after these age cut-offs were considered late onset in nature [17]. In particular, CHD included instrumental diagnosis of myocardial ischemia (ergometric EKG, scintigraphy, coronarography, others), history of acute coronary syndrome and/or treatment with percutaneous coronary angioplasty (PTCA) and/or aorto-coronary bypass.

Metabolic syndrome features overall prevalence, as defined by the third NCEP Adult Treatment Panel [12], was calculated for the FCHL subjects sample and compared with that of an age-matched free living population derived from the last Brisighella Heart Study survey [18], not taking antihyperlipidemic drugs. In order to test which MS component was significantly associated with early CV complications in FCHL patients, logistic regression was used. In the age-adjusted model other lipid factors potentially affecting the cardiovascular risk associated with FCHL were also included, such as LDL-C and Lp(a) plasma levels. The MS features were considered as categorical variables, as they are considered and defined by the ATP III guidelines for MS diagnosis [12]. This came out also by considering that, in our patient sample, 66% of men and 54% of women were under antihypertensive treatment when visited at the ambulatory service. Odds ratio were calculated for each association.

Results

Metabolic syndrome prevalence in the studied FCHL patient sample is similar to that observed in the general population (men: 25% vs. 27%; women: 31% vs. 28%; $p > 0.05$ in both cases). Distribution of the single components of the MS is also similar in the two groups.

Age is associated with early cardiovascular complications, both in men (OR: 1.0798, 95% CI: 1.05-1.11, $p < 0.0001$) and in women (OR: 1.09, 95% CI: 1.04-1.13, $p = 0.0001$).

Age-adjusted odd ratios of the association between MS (and its components) and cardiovascular complications in FCHL affected subjects are reported in Table II. None of the MS components appears to be related to cardiovascular complications in men, whilst low plasma HDL-C alone is related in women. Repeating the analysis by family clusters, these observations were maintained in the clusters larger than 4 members, but not in the smaller ones.

Among other parameters included in our analyses and not related to MS, LDL-C and Lp(a) plasma levels are only significantly associated with early cardiovascular complications in our male FCHL patient sample (LDL-C: OR 2.24, 95% CI: 1.02-4.91, $p = 0.04$; Lp(a): OR 4.64, 95% CI: 1.85-11.62, $p = 0.001$), but not in women (LDL-C: OR 1.83, 95% CI: 0.53-6.34, $p = 0.34$; Lp(a): OR 3.65, 95% CI: 0.89-14.97, $p = 0.07$). Repeating the analysis by family clusters, these observations were maintained in all clusters, independently from the number of components.

Discussion

Recent reports suggest a common etiopathogenetic link between FCHL and MS through the pathway of upstream stimulatory factor 1 (USF1) protein 1 and 2, members of the basic helix-loop-helix leucine zipper (bHLH-Zip) family of transcription factors, which includes the sterol regulatory element binding protein (SREBP) that has a well-established role in cholesterol and fatty acid metabolism [19]. From a clinical perspective, these two conditions also have some similarities. In fact, high TG and/or low HDL-C plasma levels can be found in both conditions. Both are characterized by a high plasma level of small dense LDL and by a high prevalence of overweight and/or reduced glucose tolerance [9]. A pro-thrombotic state also characterizes both conditions [20] and both are associated with an increased cardiovascular disease risk [21, 22].

Table II. Age-adjusted odd ratios of association between metabolic syndrome (and its components) and cardiovascular complications in FCHL patients who visited the Lipid Clinic of the University of Bologna from June 2003 to June 2006

Variables	Men (*n* = 636)			Wowen (*n* = 232)		
	n	OR	Sig.	*n*	OR	Sig.
Low HDL-C	384	1.00 (0.53-1.91)	0.989	68	4.50 (1.31-15.45)	< 0.001
Hypertriglyceridemia	276	0.49 (0.22-1.11)	0.088	49	0.61 (0.19-1.96)	0.410
Impaired glucose tolerance	97	0.64 (0.19-2.19)	0.479	44	0.27 (0.04-1.86)	0.186
Overweight	179	0.46 (0.18-1.15)	0.095	46	0.68 (0.23-1.99)	0.488
Arterial hypertension	510	0.93 (0.10-2.21)	0.100	191	0.98 (0.27-3.53)	0.978
Metabolic syndrome	488	1.87 (0.29-11.71)	0.502	186	0.89 (0.11-7.35)	0.920

Low HDL-C – HDL-C < 40 for men, < 50 for women; hypertriglyceridemia – TG > 150 mg/dl; impaired glucose tolerance – fasting plasma glucose > 110 mg/dl; overweight – waist circumference > 102 cm for men, > 88 cm for women; hypertension – systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg

However, there are also some characteristics which help clinicians to distinguish between the two. Namely, apoB is constantly high in FCH, but not in MS [23]. Lipid phenotype is much more variable in FCHL (more importantly, not correlated with changes in lifestyle) than in MS [24]: lifestyle is much less relevant for FCHL prognosis than for MS, as a consequence. Inheritance of the disorder is a much more evident feature in FCH; thus, clinical and laboratory manifestations are earlier than in MS [2].

From a public health point of view, the relevance of distinguishing between FCHL and MS is that the former is typically a fully inherited disease, whose prognosis is weakly modulated by lifestyle and it is even yet not evident whether the pharmacological treatments are effective in these patients (contrarily to what observed for instance in Familial Hypercholesterolemia affected ones) [25].

Furthermore, because of the high prevalence of both diseases in the general population, it is also easy to note coexistence of both conditions in the same patients. Data from the US support the hypothesis that the features of metabolic syndrome are associated with a higher prevalence of cardiovascular complications in FCHL affected subjects [13], although the absence of clear exclusion of FCHL subjects from the MS case reports allows us to suppose also that FCHL per se makes a main contribution to the strong association between MS and CHD. This appears to be true even in our population sample of strongly selected FCHL patients.

In fact, in our study MS and its main components appear not to be significantly associated with increased prevalence of early cardiovascular complications in FCHL patients, thus suggesting that the risk of developing an early cardiovascular complication is more related to the diagnosis of FCHL itself than to that of MS. Anyway, the search for MS components is relevant for the diagnosis of MS per se, but also to more correctly stratify the cardiovascular disease risk of patients who could be affected by other dyslipidemias phenotypically similar to FCHL.

However, high plasma levels of LDL-C and Lp(a) appear to be strongly associated with early cardiovascular complications in men affected by FCHL, and low HDL-C plasma levels showed an analogous association in women. We find this observation particularly interesting, because women had significantly higher baseline Lp(a) and HDL-C plasma levels than men. As for other diseases, even FCHL clinical manifestation could be strongly influenced by sex.

It may be argued that in our patient sample, MS has a relatively low prevalence compared to the general population, hypertriglyceridemia being an overlapping diagnostic factor between MS and FCH. It could be justified by an adequate selection of the FCHL patients that more specifically excluded pure MS patients.

However, our study is not prospective, so we can only find a punctual association between early cardiovascular complications and MS in FCHL patients, but not the causal role of MS in these events. This is a specific limitation of cross-sectional studies. Moreover, we did not select an age-matched sample of non FCHL-affected subjects to evaluate whether the presence of MS is more dangerous for FCHL patients than for non-FCHL subjects. Furthermore, we did not standardize the patients on the basis of their diet, which could strongly influence the lipid phenotype of both conditions [26, 27]. Another limitation of our study is that the OR calculation for association of MS components with cardiovascular complications was made considering the MS features as categorical, because of the inclusion of a large number of hypertensive subjects treated with antihypertensive drugs. However, the ATP III guidelines (on the basis of which MS was defined for this research) define them as categorical. Therefore, to the best of our knowledge, this is the first study to observe the role of MS features superposition on the cardiovascular complication rate in a large sample of Mediterranean FCHL subjects.

Further prospective studies have to be carried out to rigorously quantify the role of MS overlapping on the incidence of cardiovascular complications in FCHL affected subjects.

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