Practical guidelines for familial combined hyperlipidemia diagnosis: an up-date

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Abstract: Familial combined hyperlidemia (FCH) is a common metabolic disorder characterized by: (a) increase in cholesterolemia and/or triglyceridemia in at least two members of the same family, (b) intra-individual and intrafamilial variability of the lipid phenotype, and (c) increased risk of premature coronary heart disease (CHD). FCH is very frequent and is one of the most common genetic hyperlipidemias in the general population (prevalence estimated: 0.5%–2.0%), being the most frequent in patients affected by CHD (10%) and among acute myocardial infarction survivors aged less than 60 (11.3%). This percentage increases to 40% when all the myocardial infarction survivors are considered without age limits. However, because of the peculiar variability of laboratory parameters, and because of the frequent overlapping with the features of metabolic syndrome, this serious disease is often not recognized and treated. The aim of this review is to define the main characteristics of the disease in order to simplify its detection and early treatment by all physicians by mean of practical guidelines.
Keywords: familial combined hyperlipidemia, guidelines, diagnosis, management

Introduction

The Atherosclerosis and Dysmetabolic Disorders Study Group is an Italian research group of highly specialized lipidologists, recognized by the International Atherosclerosis Society, and continuously cooperating with different European and US research units. It is historically involved in preclinical and clinical research on genetic disorders of lipoprotein metabolism and in publication and promotion of laboratory, diagnostic, and therapeutic guidelines in this field (Lenzi et al 1986; Gaddi et al 2003). In 1994, the study group decided to set up a committee of experts on familial combined hyperlipidemia (FCH), in order to formulate a coherent description of this disorder, still largely unknown to most physicians in spite of its severity and relative prevalence. The latest report of this committee was published in 1999 (Gaddi et al 1999). Due to the rapid increase in knowledge about the physiopathology of FCH, and to the publication of further papers with diagnostic guidelines, based on different criteria, a critical update of these guidelines is now necessary.

Definition of FCH

Combining the old and the recent definitions, FCH is now defined as a common metabolic disorder characterized by: (a) increase in cholesterolemia and/or triglyceridemia in at least two members of the same family, (b) intra-individual and intrafamilial variability of the lipid phenotype, and (c) increased risk of premature coronary heart disease (CHD) (Goldstein et al 1973; Sniderman et al 2002).

In this definition other metabolic conditions with similar clinical and laboratory manifestations, such as hyperapobetalipoproteinemia, are considered (Kwiterovich 1998). Moreover, in the past FCH was also named "multiple phenotype familial hyperlipidemia", "familial mixed hyperlipidemia", "familial

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combined hyperlipoproteinemia", and "familial combined hypercholesterolemia-hypertriglyceridemia", which can be considered as synonyms of FCH.

Structure and metabolism of lipoproteins in FCH

The laboratory abnormalities most frequently found in FCH are an increase of plasma triglycerides (TG) and or cholesterol levels, and a high prevalence of small very-low-density lipoproteins (VLDLs) and/or LDLs, mainly related to an increased plasma level of apolipoprotein B100 (apo B) (Sniderman et al 2001). Some patients can present a decrease in high-density lipoprotein (HDL) cholesterol plasma level, often inversely correlated to the TG plasma level (Hokanson et al 1993).

VLDLs

An increase in the synthesis of VLDL-apo B (Venkatesan et al 1983) is usually present, but the reason why is yet to be fully understood. Some authors suggest that this increase is related to alterations in the incorporation of fatty acids in the TG (Meijssen et al 2002a) and/or alterations of the postprandial metabolism of the VLDLs, with greater conversion to small and dense LDLs and/or reduced turnover of the VLDLs themselves (Verseyden et al 2002). However, other authors showed that VLDL increase in FCH patients is mainly related to defects in activity of lipoprotein lipase (Campagna et al 2002), lecithin:cholesterol acyltransferase (Aouizerat et al 2002), and/or hepatic lipase (Pihlajamaki et al 2000). On the other hand, Evans et al (2007) recently used stable isotope techniques combined with tissue-specific measurements in adipose tissue and forearm muscle to investigate fatty acid handling by these tissues in the fasting and postprandial states of FCH patients. They found that the major defect appeared to be overproduction of triacylglycerol (TAG) by the liver due to decreased fatty acid oxidation, with fatty acids directed to TG synthesis, while evidence of decreased lipoprotein lipase action or impaired fatty acid re-esterification in adipose tissue was observed.

An impaired postprandial plasma component C3 response has been observed in FCH patients, most likely as a result of a delayed response by C3, as the precursor for the biologically active acylation-stimulating protein, acting on free fatty acid (FFA) metabolism (Meijssen et al 2002b). Therefore, an impaired postprandial C3 response may be associated with impaired peripheral postprandial FFA uptake and, consequently, lead to increased hepatic FFA flux and VLDL overproduction (Meijssen et al 2002a).

In FCH patients, the VLDL TG content is inversely related to the LDL-C plasma level: the redistribution of apoB and plasma cholesterol could be a key process in development of various phenotypes. The plasma apoB and cholesterol in VLDL particles, when in abundance, are associated with significantly lower cholesterol levels in the bigger and more buoyant LDL particles. This effect is reversible by reducing plasma TG levels (by diet, by drugs, and/or by physical activity), which in turn may result in redistribution of apoB and TC from the VLDL particles to LDL particles (Ayyobi et al 2003).

In a recent study, de Graaf et al (2007) point to high remnant-like particles cholesterol (RLP-C) as a potential biomarker of FCH. In fact they observed that patients with FCH have 2-fold elevated plasma RLP-C levels, which add to the atherogenic lipid profile and contribute to the increased risk for cardiovascular disease (CVD). Plasma RLP-C levels above the 90th percentile predicted prevalent CVD, independently of non-lipid cardiovascular risk factors (odds ratio 2.18 [1.02–4.66]) and TG levels (odds ratio 2.35 [1.15–4.83]). However, in both FCH patients and controls, RLP-C did not provide additional information about prevalent CVD over and above non-HDL cholesterol levels).

LDL

There is a predominance of small and dense LDLs (so-called atherogenic LDL "B" pattern), poor in cholesterol, and thus with a high apo B/cholesterol ratio. The main determinants of LDLs size appear to be the TG and HDL-C plasma levels (Vakkilainen et al 2002).

The synthesis of LDL-apo B increases due to uncontrolled overproduction of apo B (Kissebah et al 1984). No major alterations in the LDL liver catabolic rate have been described: in FCH patients, the activity of the LDL receptor (with a high affinity for apo B100) is normal (Kane et al 1989). The reduction in lipid levels after diet and lipid-lowering drugs does not normalize the kinetic and structural characteristics of the LDLs, at least in a large percentage of patients (Meijssen et al 2002a). Some studies suggest that a relative deficit of hepatic lipoprotein lipase can reduce the liver uptake of apo B to simulate the increased synthesis of these apolipoproteins (Williams et al 1991).

Moreover, LDL from FCH patients, irrespective of lipid phenotypes, are more susceptible to oxidation in vitro than LDL from healthy controls. This increased susceptibility of LDL to oxidation in vitro seems to be a consequence of the abundance of small dense LDL particles and not to defects of antioxidant capacity in FCH (Liu et al 2002). In FCH patients with very high LDL-C plasma levels of lipoprotein (a) may be high as well (Cicero et al 2003).

HDLs

Reduced levels of HDL-C are a frequent finding in FCH patients. HDL-C and HDL2 reduction could be due to TG-enrichment of HDL particles and enhanced hepatic lipase (HL), while the role of lipoprotein lipase (LPL) and activities of cholesterol ester transfer protein (CETP) and phospholipid transfer protein (PLTP) appears to be less evident (Soro et al 2003). Recent data suggest that HDL-C values are lower in subjects with predominantly small and dense LDL and are associated with a very high concentration of VLDL-1 (with low apo AI and apo E content). LDL pattern is suggested to be the main determinant of the phenotype expressed by FCH patients (Georgieva et al 2004).

Genetics

FCH was initially suggested to have a dominant monogenic mode of inheritance (Austin et al 1990). Later, some authors hypothesized a more complex inheritance to explain the variability in the lipid phenotype. Pajukanta et al (1998) identified a locus linked to FCH on 1q21-q23 in Finnish families with the disease. This region has also been linked to FCH in families from other populations (Coon et al 2000; Peri et al 2000; Allayee et al 2002) and to type 2 diabetes mellitus (Elbein et al 1999; Wiltshire et al 2001). These clinical entities have some overlapping phenotypic features, raising the possibility that the same gene may underlie the obtained linkage results.

Linkage studies and association analysis suggested that the association of the newly discovered apo AV gene with APOAI/CIII/AIV cluster contributes to FCH transmission in a case report of 128 European families (Eichenbaum-Voline et al 2004).

Other authors proposed that LDL size in FCH patients is a trait influenced by multiple loci located to 9p, 16q, and 11q (Badzioch et al 2004).

Recently, the gene encoding upstream transcription factor 1 (USF1) has appeared to be specifically linked to FCH in 60 extended families with FCH, including 721 genotyped individuals, especially males with high TG. USF1 encodes a transcription factor known to regulate several genes controlling glucose and lipid metabolism. The concept that USF1 affects the complex lipid phenotype of FCH, and not only one lipid trait, is supported by the findings of the same authors on allelic associations of the usf1s1-usf1s2 risk haplotype with TG, apo B, TC, and LDL peak particle size (Pajukanta et al 2004). This finding might explain both the "monogenic"-like transmission of the trait and the intra-individual and intra-family variability of the phenotype.

However, the gene–environment interaction could strongly influence the laboratory and clinical features of FCH (Stalenhoef 2002; Corella and Ordovas 2005), complicating the disease detection by all physicians, and also by specialized lipidologists.

Prevalence

FCH is very common and is considered one of the most common genetic hyperlipidemias in the general population (prevalence estimated: 0.5%–2.0%), being the most common in patients affected by coronary diseases (10%) and among acute myocardial infarct survivors aged less than 60 (11.3%) (Gaddi et al 1999). This percentage increases to 40% when all the myocardial infarct survivors are considered without age limits (De Bruin et al 1996).

Prevalence estimates, on the other hand, strongly depend on the diagnostic criteria adopted; applying the most accepted ones to the free-living adult cohort of the Brisighella Heart study, we estimated a 2.8% prevalence of FCH, although some patients with metabolic syndrome or random association of other genetic factors may have contributed to prevalence overestimation (Cicero et al 1999). From data obtained on 1190 Japanese children a prevalence of 0.4% was calculated, suggesting that at least half of all individuals with FCH already demonstrate hyperlipidemia in childhood (Iwata et al 2003).

No other differences are apparent, but geographical distribution is not known, since the main studies carried out so far consist only of Caucasian patients living in Europe or in the US.

According to a conservative estimate (whole population: 0–99 years), over 3.5 million subjects are affected by this disorder in EU (and 2.7 million in the US); it is the cause of approximately 30,000–70,000 infarcts/year in the EU (and more or less the same number in US), often premature (Gaddi et al 1999).

Because of the lack of agreement among researchers, and because of the intrinsic characteristics of the disease to appear in different moments with different phenotypes, it is often hard to obtain good epidemiological data on its real prevalence and to distinguish FCH from the metabolic syndrome and from patients with random clustering of genetic factors simulating the FCH phenotypes.

Clinical aspects

A high degree of diagnostic uncertainty exists in the categorization as normal or abnormal of members of FCH kindred (Aguilar Salinas et al 2004). This observation was clearly

confirmed by a recent 5-year follow-up study showing how up to 40% of patients can be misclassified based on a single observation (Veerkamp et al 2002). Different diagnostic criteria would result in conflicting results. This is a critical issue: depending on the diagnostic criteria used, completely different conclusions could result from the linkage analysis in the FCH studies (del Rincon Jarero et al 2002). Recently, an interesting nomogram for FCH detection has been proposed by Veerkamp et al (2004).

The nomogram is easy to use especially for general practitioners, even if some concerns about its wide applicability are that in FCH, by definition, the values of TG and TC are strongly variable (in long, medium, and short periods); thus a fixed percentile cut-off may be difficult to use. Moreover, we have no data on periodical prevalence of the disease to elaborate a mixed time-percentile index. Then, percentiles of cholesterolemia and triglyceridemia are not available for all populations and the use of specific values different from those suggested for diagnosis and therapy for the general US/EU population (IAS 2003) may be really confounding for physicians. Using percentiles or nomograms, a high diagnostic overlap with other genetic hyperlipidemias may also occur, mainly due to the exclusion of the lipid phenotype variability as a main diagnostic criterion of FCH that could over-estimate the FCH prevalence in the population.

Another problem to be considered is that the laboratory manifestation of FCH could remain relatively silent until some events occur. In particular body weight increase appears to be strongly related to lipid modification that could be observed in FCH patients (Koprovikova et al 2006). In fact, waist-to-hip ratio appears to be the best determinant of hyperlipidemia, particularly hypertriglyceridemia in FCH patients (van der Kallen et al 2004). This is particularly evident in children affected by FCH (ter Avest et al 2007a) and it could be related to insulin resistance (Veerkamp et al 2005), and decreased plasma levels of adiponectin (van de Vleuten et al 2005a) and decreased levels of leptin (van de Vleuten et al 2005b).

FCH diagnosis is very complex in children, too, because of the lack of long-term data linking lipid values measured before 12 years to the expression of the disease in the adult state or in the old people. In any case, for children, too, Kuromori et al (2002) suggested avoiding cut-off points based on a given percentile, and suggested clarifying the family history and measuring lipid profiles in the parents (Kuromori et al 2002). Hyperapo B in children may be a precursor of other lipid abnormalities, and thus it suggested as a good marker of early diagnosis of FCH (Kuromori et al 2002).

In the present revision of the diagnostic criteria, we take into account that: (1) recent data indicate that "specialists try to 'pull' cases toward their specialty" (Hashem et al 2003), causing an impressive number of severe diagnostic medical errors; (2) in the long-life asymptomatic phase of FCH (before CHD) the diagnosis might be strongly underestimated; (3) as far as possible, the diagnostic cut-off points should be identical to those suggested for risk stratification in the general population, at least for Caucasians; and, (4) laboratory diagnostic methods should be easy, not expensive, and easily reproducible.

The following considerations are discussed:

Inherited hyperlipoproteinemia (LDL-C $>$ 160 mg/dL and/or TG $>$ 200 mg/dL)

Often in FCH the HDLs are reduced ($<$40 mg/dL); yet we do not have sufficient evidence to suggest the use of this parameter in FCH diagnosis (De Bruin et al 1996). The LDL-C and TG cut-offs are also the "normal" limits suggested by the more recent report of the National Cholesterol Education Program (NCEP ATPIII) (Adult Treatment Panel III 2001). It is evident that the higher the number of samples taken and of family members studied, the better the diagnostic sensitivity and specificity. It can be estimated that around 20% of the adult population will have values above these cut-off points; but the percentage drops to around 3% when both parameters (LDL-C and TG) are considered together and secondary hyperlipoproteinemias are excluded, and to even lower levels if the evaluation of the intra-individual variability over a period of time and intrafamilial variability are included. The final estimates (1%–2%) correspond to the estimated prevalence of FCH in the adult population (Cicero et al 1999).

Hyperlipoproteinemia B

High plasma level of apo B ($>$125 mg/dL) is one of the best diagnostic and prognostic factor for FCH adults (Demacker et al 2000; Sniderman et al 2002; de Graaf et al 2004), and for children (Kuromori et al 2002; Sveger and Nordborg 2004). Therefore, dosing with plasma lipid is required where specialized laboratories are available. However, in many countries the apoB dosage is not standardized and often not widely available, except where highly specialized laboratories are available: this is the reason it is reasonable to reserve the dosage of apoB to a second level diagnosis in specialized Lipid Clinics. Moreover, the most correct approach to indicate a diagnostic cut-off point is to choose a specific percentile of each considered laboratory value for that population. Therefore, there is still a large lack of

epidemiological data on plasma apo B distribution in different populations and age classes, so that its interpretation in not easy nor univocal for the non specialist physician.

Primitive variability of the lipid phenotype

The propositus could present hypercholesterolemia, hypertriglyceridemia, both, or even a "normal" phenotype at different times. The variability is rarely fast, and could be observed only during a long observational phase (several months) (Delawi et al 2005). Because both LDL-C and TG are not necessarily high in FCH patients, it is plausible that values considered as borderline high by the ATP III guidelines (LDL-C > 130 mg/dL and/or TG > 150 mg/dL) (Durrington 2004) could be useful to evaluate the intra-individual variability of the lipid phenotype. The propositus could even have a constant phenotype (mainly IIb phenotype), and family members could have a different phenotype (ie, an isolated rise in LDL-C or in TG plasma level) (Ylitalo et al 2002). If patients are already treated with antihyperlipidemic drugs, it could be necessary to give confidence to the pre-treatment values (if available). However, to the best of our knowledge, no antihyperlipidemic treatment is able to stabilize the lipid phenotype variability of FCH patients, so that it is maintained if the drug dosage is stable.

Biomarkers of early atherosclerosis

Increased carotid artery intima-media thickness (IMT) was recently proposed as an adjunctive diagnostic parameter, able to distinguish better between affected and non-affected members in the same family (Ylitalo et al 2002). The strength of association is obviously higher if we observe patients already affected by an early coronary or cerebrovascular event or with a family history of early cardiovascular events. Members of FCH families showed impaired FMD, which was independently associated with markers of insulin resistance (Karasek et al 2006). The group of De Graaf, historically involved in research on FCH, recently also demonstrated that FCH patients have also increased pulse wave velocity and reduced flow mediated dilation, both markers of arterial stiffness and endothelial dysfunction. However, the same group showed that adding these parameters to the traditional stratification of cardiovascular risk did not increase the prediction ability, so they raised some doubts about the diagnostic utility of endothelial dysfunction markers in conditions such as FCHL a priori characterized by an elevated cardiovascular disease risk (Ter Avest et al 2007b, c). Some laboratory parameters have been also proposed, but until now no one has demonstrated a specific biomarker for FCH. Further research is needed in this field.

Other clinical features

The correlation between fatty liver and non-alcoholic steatohepatitis (NASH) and metabolic disorders of triglycerides, LDL-C, and insulin resistance is well known, and is very complex (Sveger et al 2004). NASH prevalence is higher particularly in patients with metabolic syndrome (Green 2003). Recently, De Bruin et al (2004) reported the presence of non-alcoholic fatty liver also in patients with FCH. At present, this important clinical finding is not useful for FCH diagnosis or for differential diagnosis (see later). Xanthomatous phenomena are very rare in this disorder (Kane et al 1989), although other simultaneous anomalies, such as the presence of peroxides in LDL and high Lp(a) plasma concentrations, could represent a triggering factor in the expression of xanthomatosis in sporadic cases (Mancuso et al 1996).

In the setting of general medicine, the following diagnostic criteria are thus suggested for FCH:

First level diagnosis

1) In the patient: primary hyperlipoproteinemia (LDL-C > 160 mg/dL and/or TG > 200 mg/dL), PLUS
2) In the patient and in at least one member of the family: primary variability of the lipid phenotype (hypercholesterolemia, hypertriglyceridemia, both, or even a "normal" phenotype) evaluated on the basis of at least 3 consecutive (bimonthly) controls (the repetition of lipid analysis before to define a diagnosis of dyslipidemia is in agreement with the international guidelines) (Adult Treatment Panel III 2001).

Second level diagnosis (specialized labs only)

1) Evaluation of apo B100 plasma level: preferably by standardized immunoturbidimetric assay (NHANES Group 1994)
2) Detection of small and dense LDL particles (LDL pattern B): there is not yet a standardized method to dose small dense LDLs; different methods have been tested (from preparative and non-equilibrium density gradient ultracentifugation to nuclear magnetic resonance) but the most frequently used is the gradient gel electrophoresis (Rizzo and Berneis 2006)
3) Genetic tests to exclude similar more rare forms of familial dyslipidaemias, when indicated (unclear situations, suggestive clinical and laboratory condition)

Specific cases

If family data are not available, the presence of unexplained (primary) IIb phenotype (eg, not related to significant change in dietary habits or body-weight gain or by an evident double

heterozygosis for familial hypercholesterolemia and familial hypertriglyceridemia) may suggest the diagnosis (Gaddi et al 1999). The presence of early onset atherosclerosis (IMT included) and/or clinical complications (CHD/CVD/POAD) in the patient and/or in relatives (probably carriers of the disease on the basis of genealogical tree) is not strictly diagnostic of FCH, but it could suggest an aggressive dyslipidemia or, in any case, a condition at high risk of cardiovascular disease. Lipid abnormalities (including presence of small and dense LDL) in non-controlled diabetes will be regarded with caution and have to be re-evaluated after improvement of diabetes control.

Differential diagnosis against metabolic syndrome

The recent enlargement of diagnostic criteria for metabolic syndrome (MS) proposed by the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol (Adult Treatment Panel III 2001) has caused a significant overlap with the diagnosis of FCH. MS was identified in 65% of FCH patients compared with 19% in controls without FCH (odd ratio: 3.3, $p < 0.0001$). The increased prevalence of the MS alone could account for a significant part of the elevated CHD risk associated with FCH (Hopkins et al 2003) as well as the high prevalence of FCH among patients diagnosed, as MS produces an overestimate of CHD-risk in MS.

Common features between the two pathological conditions are:

- Frequent hypertriglyceridemia and/or low plasma HDL-C level
- Frequent association with non-lipid cardiovascular risk factors as blood hypertension, abdominal obesity, reduced glucose tolerance/diabetes
- Strongly increased cardiovascular disease risk

The main differences between the two conditions are:

- Apo B is constantly high in FCH, but not in MS. LDL-C values are usually normal or rather low in MS.
- The lipid phenotype is more variable in FCH than in MS (both in individuals and families)
- The inheritance of the disorder is much more evident in FCH, and life style is much less relevant on FCH clinical manifestation and prognosis than on MS
- Earlier clinical and laboratory manifestation in FCH than in MS
- Low grade inflammation (eg, high plasma level of hsCRP, adhesion molecules) and/or procoagulative conditions (eg, high plasma level of fibrinogen, PAI-1) have been more frequently associated with MS (Gaddi and Cicero 2006)

The clinical picture and associated complications/conditions (atherosclerosis, NASH, diabetes, hypertension) are not useful for differential diagnosis. In particular, overweight and insulin-resistance, that are main factors involved in the pathogenesis of MS, are strongly associated to the plasma lipid change observed in FCH patients (de Graaf et al 2004; Veerkamp et al 2005).

Recently, Ayyobi and Brunzell (2003) suggested that severe lipid abnormalities are more frequently caused by FCH rather than by diabetic hyperlipidemia or MS. This is a simplified point of view that does not take into account the typical phenotypic variation of FCH, which also determines a wide range variation of laboratory parameters, from very high to very low levels. Moreover, also in non-controlled diabetes and in patients with multiple-causes of hyperlipoproteinemia (example: insulin-resistance syndrome plus ε4 homozygous or heterozygous plus LPL deficit) lipid values may rise to very high levels.

The marked variability of lipid profile, not explained by diet or body-weight variations, might represent the best diagnostic criterion to reduce the overlapping between MS and FCH. Severity of lipid alteration, constant presence of pattern B LDL, and/or of high apo B plasma level (favoring FCH diagnosis), or presence of abdominal obesity and insulin resistance (favoring MS) could orientate the differential diagnosis, but do not prove it.

As already above stated, lacking a specific laboratory or clinical marker of FCH, the final diagnosis in patients with MS features could be often difficult, especially in those subjects with insufficient laboratory documentation, already taking antihyperlipidaemic drugs, and/or diabetics. However, from a practical point of view, if patient is diabetic the differential diagnosis with FCH could not be so relevant, because diabetic patients have to be already treated to reduce to the minimal level their cardiovascular disease risk independently from the baseline plasma lipid (American Diabetes Association 2006). Therefore, in these patients it remains relevant to adequately monitor the plasma lipid level of the younger non-diabetic family member in order to eventually diagnose FCH early.

Prognosis

FCH is definitively very frequent in patients affected by CHD. In the general population, the spontaneous variability of lipid phenotype appears to be associated with an increased risk of cardiovascular disease (Cicero et al 2000). Until now,

no adequately designed trials on FCH patients have been carried out to estimate their peculiar cardiovascular disease risk. Some authors suggest that it is at least as elevated as that of heterozygous familial hypercholesterolemia patients (Skoumas et al 2006). FCH is clearly also a risk factor for increased carotid artery intima-media thickness (IMT): the increased IMT observed in FCH patients corresponds, on average, to a 7-year increase in IMT (Keulen et al 2002). The parameter best correlated with IMT is the plasma apo B level and consequently the LDL particle size (but not LDL susceptibility to oxidation) (Liu et al 2002). A worse prognostic factor appears to be the constant association of hypercholesterolemia to hypertriglyceridemia: young people with this kind of lipid phenotype have a reduced coronary flow reserve during hyperemia compared with age-matched hypercholesterolemic not hypertriglyceridemic subjects (Pitkanen et al 1999). Hypertriglyceridemia per se appears in fact to be a significant predictor of cardiovascular disease in proportion to the baseline TG levels (Austin et al 2000).

We suggest considering FCH patients at very high CHD and CVD risk, as confirmed by family studies (Goldstein et al 1973; Sniderman et al 2002; Ayyobi and Brunzell 2003); specifically, it is necessary to point out that risk estimates based on risk charts, scores, or functions used in the general population, probably grossly underestimate the real risk of the FCH patient, and must be avoided.

FCH patients management: practical guidelines

The main first-line vascular diagnostic approach to be considered is the carotid ultrasound with morphometric evaluation of the lesions, because it is highly predictive of future cardio- and cerebro-vascular events, and is inexpensive, not invasive, and easily repeatable (O'Leary and Polak 2002). IMT/ultrasound examination should also be performed, when possible, on other districts (aorta, ileo-femoral arteries, etc). The control of silent myocardial ischemia could be performed with the same diagnostic flow chart recently suggested for familial heterozygous hypercholesterolemias (Civeira 2004); diagnostic algorithms specific for FCH are not yet available.

With regard to drug therapy, some small clinical trials have been conducted on patients defined as affected by "combined" or "mixed" hyperlipoproteinemia (Forster et al 2002; Wang et al 2003; Grundy et al 2005). Other small trials conducted on subjects selected as being affected by FCH suggest some efficacy of statin (Blanco-Colio et al 2004; Sirtori et al 2005), fibrates (Bredie et al 1996), omega 3 polyunsaturated fatty acids (Tato et al 1993), and thiazolidinediones (Abbink et al 2006) on secondary outcomes (eg, endothelial function, LDL composition, oxidation markers, inflammation markers). Atorvastatin and fenofibrate displayed comparable efficiency in decreasing oxysterols, but they decreased lipid-corrected alpha-tocopherol levels in plasma, which are already low in FCH patients (Arca et al 2007). However a full-dosage of a powerful statin such as rosuvastatin was not able to improve endothelial function of FCH patients (ter Avest et al 2005). Moreover, pioglitazone 30 mg/day in patients on conventional lipid-lowering therapy acts favorably on several metabolic parameters, such as TG/HDL (atherogenic index of plasma [–32.3%, $p = 0.002$], plasma glucose [–4.4%, $p = 0.03$], alanine-aminotransferase [ALT] [–7.7%, $p = 0.005$], and adiponectin [130.1%, $p = 0.001$]) (Thomas et al 2007). Thus, lacking specific long-term data on drug efficacy on strong outcomes of FCH patients, the main proposed recommendations for FCH therapy are based on the results obtained from long-term clinical trials with hard outcomes on cardiovascular morbidity and mortality. However, the majority of available trial analyses are on the same group of patients with FCH, with mixed/multigenic hyperlipoproteinemia (from random association of different genetic factors in the same subjects), metabolic syndrome, secondary hyperlipoproteinemia, etc, and data obtained might be not strictly representative of the effect of tested drugs/lifestyle changes on FCH patients.

In any case, the effectiveness of statins to reduce cardiovascular risk suggests that these drugs should be the first-line treatment for FCH also (Bays and Stein 2003), perhaps with a preference for those with a stronger triglyceride-lowering activity (Verseyden et al 2004). The triglyceride-lowering effect, which is mainly through an increase in the hepatic reuptake of VLDL, ILDL, and LDL is, however, less than that of fibrates, which increase lipoprotein lipase activity by a mechanism involving peroxisome proliferators activator receptors alpha and gamma (Insua et al 2002).

The fibrates' cholesterol-lowering effect is, however, smaller than that of statins. Omega-3 polyunsaturated fatty acids also lower VLDL triglycerides, slightly increasing LDL-C and HDL-C (Calabresi et al 2004). The association of statins with drugs more active on TG plasma levels (omega-3 polyunsaturated fatty acids, fibrates, nicotinic acid) could be an efficacious way to treat this kind of patients (Grundy et al 2005; Koh et al 2005). Ezetimibe, a selective inhibitor of the bowel cholesterol adsorption, might be an optimal drug to be associated to statins or fibrates instead of the prescribed resins (Jeu and Cheng 2003).

Slow-release nicotinic acid is another very interesting and plausible therapeutic weapon to be associated to the standard statin and/or to fibrate therapy (Elam et al 2000); probably, the dose-dependent effects of nicotinic acid derivatives and the good safety and interaction profiles, will open a new therapeutic approach even for more severe (and drug-resistant) FCH patients.

In the absence of data on long-term effects of different therapies on the prognosis of FCH patients we suggest: (a) monitoring the therapy not only by lab tests, but also by evaluating IMT and other instrumental and clinical markers of CHD, and (b) following the theory of "the lower, the better", treating these patients in order to reduce their cholesterolemia and triglyceridemia to the best goals suggested by the international guidelines for cardiovascular diseases prevention (Adult Treatment Panel III 2001), in association with a rigid control of all associated risk factors. The practitioner has to be advised that escape phenomena and variability of lipid phenotype might represent a major source of bias in analyzing the efficacy of therapy.

The high prevalence of FCH and MS in the US and EU suggests that the first-level diagnosis and the basic therapeutic strategy have to be prescribed by family physicians and/or by wide spread territorial specialized units. In this context, we think that the above suggestions, combined with the widely known recommendations of the ATP III (Adult Treatment Panel III 2001), will help easier early detection of patients likely to be diagnosed with FCH and of patients in general at high risk of cardiovascular disease.

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