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PATIENTS WITH COMBINED HYPERLIPIDEMIA

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Combined Hyperlipidaemia or Familial hypercholesterolemia (FH) is a frequent genetic disorder viz., an autosomal codominant disorder, characterized by elevated low-density lipoprotein (LDL)-cholesterol (LDL-C) levels and early onset of atherosclerotic cardiovascular disease[1]. The expression of the genetic potential for these lipid disorders is a complex process which only occurs when genetically inherited predisposing factors interact with other metabolic factors that exacerbate hyperlipidaemia[2]. Adipose tissue secretes several adipocytokines (i.e. adiponectin, leptin, and others) that regulate appetite, immunity, inflammation, and glucose/lipid metabolism[3]. Basically, hepatocytes and steroid hormone-producing cells have LDL receptors. Normally, these cell surface receptor for LDL removes cholesterol-carrying LDL from the plasma by a process of receptor-mediated endocytosis. However, mutations in the LDL receptor gene results in FH[4]. FH is caused by mutations in genes that regulate LDL catabolism, mainly the LDL receptor (LDLR), apolipoprotein B (apo B), and gain of function of proprotein convertase subtilisin kexin type 9 (PCSK9). However, the phenotype may be encountered in individuals not carrying the latter monogenic defects, in approximately 20% of these effects of polygenes predominate, and in many individuals, no molecular defects are encountered at all. These so-called FH phenocopy individuals have an elevated atherosclerotic cardiovascular disease (CVD; ASCVD) risk in comparison with normolipidemic individuals but this risk is lower than in those with monogenic disease [1].

Currently, three genes are known that can result in the phenotype of FH when affected by a mutation: the LDLR, apoB, and proprotein convertase subtilisin/kexin type 9 (PCSK9) [5]. The receptor defect reduces the catabolism of LDL by around 50% and results in an approximately two-fold elevation in plasma LDL-C. The excess plasma LDL-C deposits in tendons and arterial walls, forming tendon xanthomas and atherosclerotic plaques. The most important clinical feature of untreated FH is the development of premature and extensive atherosclerosis leading to coronary heart disease (CHD). Clinically overt CHD usually occurs at the mean age of 45–48 years in males and 55–58 in females [4]. The clinical phenotype resulting from these mutations is variable, but in essence, consists of increased levels of LDL-cholesterol (LDLC) and premature coronary heart disease (CHD). Homozygous FH is much less common[4]. If left untreated, FH patients, in general, have a 3-4 times higher risk for CHD compared to unaffectedsubjects, and CHD events can occur one decade earlier [5]. The high levels of apoB and a predominance of small dense LDL particles are the markers of atherosclerotic burden.

In subjects with FH, the development of atherosclerosis is thought to be associated with an overproduction of liver-derived apolipoprotein B (in very-low-density lipoproteins (VLDLs), an abnormal VLDL particle composition, and a reduction in lipoprotein lipase (LPL) activity. The severity of dyslipidaemia associated with FH can be evaluated by measuring some of these features. Variables that may regulate the phenotypic expression of FH include hyperinsulinemia, the plasma concentration of several apolipoproteins, genetic factors, and inflammatory mediators.

Hyperinsulinemia is a well-known factor to regulate apo B containing lipoprotein synthesis and catabolism. However, its role as a determinant of the severity of dyslipidaemia is controversial, as only around 50% of FH subjects have hyperinsulinemia[3].

The diagnosis of FH is a critical one to make, given the high risk of morbidity and mortality from premature CHD. The clinical diagnosis of FH has traditionally been achieved using typical clinical traits. Hypercholesterolemia is present from birth in the majority of heterozygous FH patients and most will have an LDL-C well above the 90th percentile for age (approximately 190 mg/dl for adults). For diagnostic purposes, LDL-C levels of 260 mg/dl or higher in individuals aged 40 years or older (with lower cut points in younger subjects) are sought with clear evidence of dominant transmission or tendon xanthomas within the family. In addition to elevations in LDL-C, FH patients typically present with a normal serum triglyceride (TG) level, no secondary causes of hypercholesterolemia (e.g. hypothyroidism, hepatic disease or diabetes), a family history of elevated serum LDL-C and early coronary atherosclerosis. Heterozygous FH patients may develop tendon xanthomas and/or corneal arcus from the age of 10 years although these traits are insensitive markers. The clinical manifestation of homozygous FH is markedly different from that of the heterozygous form of the disease. Severe hypercholesterolemia (LDL-C ranges from 600 to 1200 mg/dl) is present from birth and persists throughout life. Tendinous and tuberous xanthomas, corneal arcus, and generalized atherosclerosis typically develop in homozygotes by the age of 4 years[4]. The molecular genetic diagnosis is important to establish the homo- or heterozygous genetic state of the patient. If complete family lipid level data are available, diagnosing heterozygous FH is usually relatively simple due to the clear clinical picture of the disease and the bimodal distribution of LDL-Cwithin the affected family. In comparison, identifying an isolated heterozygous FH case in the general population can be rather arbitrary, particularly in the absence of family lipid data[4]. Prompt diagnosis and aggressive treatment are critical to the long-term survival of FH patients. Despite the high levels of morbidity and mortality associated with FH, the disease remains considerably underdiagnosed and under-recognized. Underdiagnosis of FH denies patients the early treatment that may reduce their risk of developing premature CHD[4]. Once identified, FH homozygotes should begin drug therapy as soon as possible. Early detection and treatment of FH are critical to prolong the life of these patients. FH heterozygotes can be placed on a diet and drug management program[6].

In FH, the usually recommended diet and lifestyle modifications do not achieve the target LDL- cholesterol concentrations advised by US National Cholesterol Education Program. However, many of the drugs found to be effective in treating adults with this disease are not licensed for use in children; therefore, diet is the main treatment for children with FH. he recommended diet includes lower cholesterol intake but also, lower intake of saturated fatty acids since saturated fatty acids seem to suppress LDLR activity. This diet limits saturated fat intake to <7% of total caloric intake and

cholesterol intake to <200 mg/d. Thus, diet can lead to a reduction of total plasma cholesterol but the combination with bile acid-binding resin therapy has even better results in heterozygous FH children. In addition to the cholesterol-lowering diet, several other dietary interventions have been suggested as some nutritional supplements (pectin, polyphenols, and phytosterols). Phytosterols seem to represent the most effective supplementation [6].

Since patients with FH are at significantly increased risk for developing coronary heart disease, treatment to correct abnormal levels of plasma lipoproteins theoretically should reduce their coronary risk. Ideally, therapy would be directed toward the underlying overproduction defect. Decisions for the treatment of elevated lipids mainly focus on low-density lipoprotein cholesterol (LDL-C) level as well as the cardiovascular risk status of the individual[7]. In patients with FH, therapeutic management is a cornerstone for the prevention of cardiovascular disease. The recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines and National Lipid Association (NLA) recommends that a 50% relative reduction in LDL-C provides the best benefit in terms of cardiovascular risk reduction. In clinical practice, the maximal reduction of LDL-C should be considered using appropriate drugcombinations in tolerated doses[8]. Statins (inhibitors of ß-hydroxy-ß-methylglutaryl coenzyme A reductase) are the drugs of the first choice in patients with FH. The regulatory response to these drugs is to increase LDLR expression, which in turn leads to decreased plasma LDL levels. However, the lipid-lowering effect of statin treatment in FH patients presents significant variation, most likely depending on the type of LDLR mutation. Also, nicotinic acid appears to predominately decrease the hepatic production of lipoproteins, lowering levels of both very- low-density lipoproteins (VLDL) and low-density lipoproteins (LDL). Unfortunately, nicotinic acid can cause several side effects that may limit its use[7]. Therefore, many patients require combination therapy to achieve the desired cholesterol concentrations[6].

Currently, a combination of five major classes of drugs, with statins, is being used to treat FH. These strategies include:

- The antisense oligonucleotides directed at apolipoprote in B,
- The protein convertase subtilisin/kexin type 9 inhibitors (PSCK9),
- The microsomal triglyceride transfer protein (MTP) inhibitors,
- The cholesteryl-ester transfer protein inhibitors,
- The thyroid mimetics.

However, several new therapeutic strategies are under development. Antisense therapy with Mipomersen seems to hold a promise as a potential therapeutic option for patients with severe hypercholesterolemia not adequately controlled on currently available lipid-lowering medications. Clinical trials have shown the drug to be highly effective and safe as a lipid- lowering agent when used as monotherapy or in conjunction with stable statin therapy. Still, however, long-term cardiovascular outcomes studies with this therapy need to be carried out. Microsomal triglyceride transfer protein inhibitors seem to exert anti-atherosclerotic and insulin-sensitizing effects. Thus, future indications for intestine-specific microsomal triglyceride transfer protein inhibitors may include dyslipidaemia associated with insulin- resistant states, familial combined hyperlipidaemia, and homozygous familial hypercholesterolemia. The β thyroid hormone agonists viz., thyroid analogs, with additional tissue-specific effects and with higher selectivity to β thyroid receptor, may lead to improved safety and efficacy and allow for their application to hyperlipidaemias. Thyroid mimetics may prove useful in combination not only with statins but also with HDL-C increasing drugs such as fibrates or nicotinic acid. As a novel therapeutic strategy, they may not simply lower LDL-C, but may also reduce pre-existing plaques through the promotion of reverse cholesterol transport. Despite improvements in lipid-lowering therapy during the last decades, familial hyperlipidaemia still remains a substantial contributor to cardiovascular disease, as the treatment goals with current lipid-lowering therapy are not achieved in a significant number of patients[8]. Only a small proportion of patients with FH reach the LDL cholesterol treatment target, so there is a need for new treatment options in FH subjects in order to further decrease the LDL-cholesterol levels. Gene therapy for FH could be used to decrease the morbidity and mortality in these patients. Liver transplantation has also been found to be an effective treatment for FH[6].

CONCLUSION

Despite an extensive screening program spanning over twenty years, a substantial proportion of the FH patients are still undiagnosed and therefore undertreated. It remains a continuing challenge to screen and identify FH patients. The high CHD risk in these patients is currently being kept under control with drugs like statins, but a substantial residual CHD risk remains. Though there has been a great evolution in FH knowledge and treatment modalities in the last decade, the reality evolving its care is far from ideal. Public health policies for improving diagnosis, cascade screening, and treatment should be implemented. Physician and patients' education programs could in part attenuate the problems around FH care. Novel combination therapies along with possible use of gene therapy may further help to strengthen the existing therapy for the better management of FH.

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