PREVENTION OF CARDIOVASCULAR EVENTS IN CHILDREN

Renata Auricchio

Principal investigator
Renata Auricchio

Other components of the research group
Luigi Greco
Michela Proto
Serena Spigno

Background

Familial hypercholesterolemia (FH) is one of the most common, but underdiagnosed, autosomal dominant disease. It is characterized by an increase in LDL cholesterol (LDL-col) levels from birth, with a consequent acceleration of the atherosclerotic process and increased risk of premature cardiovascular disease (CVD). The most recent data indicate a prevalence of the heterozygous conditionaround 1 in 200/250 in general population, by genetic screening carried out in the Northern Europe. Before the prevalence of FH was estimated around 1: 500. Affected patients have a 10-fold increased risk of developing CVD, compared to unaffected subjects, due to lifelong exposure to high levels of LDL-col. Therefore, the early identification of subjects with FH is essential to minimize the impact of long life hypercholesterolemia and to prevent or at least delay the onset of cardiovascular events, through a nearly start of lipid-lowering therapies (statine) also in pediatric age (>6 years). If untreated, heterozygous FH (HeFH) develop CVD respectively before the age of 55, while homozygotes (HoFH) can manifest it even in the first years of life and, if not treated, could die sooner than 20 years.

The genes mainly associated with FH are: LDL receptor (LDLR), APOB, which encodes for a protein involved in the function of LDLR, and PCSK9, proprotein convertase serine-kexin of type 9, involved in the degradation of LDLR. LDLR is the most frequently mutated gene and to date more than 1500 causative FH mutations have been described.

The diagnosis of Familial Hypercholesterolemia still remains a common problem in many European and non-European countries. Currently in Europe the only country where a universal pediatric screening program for Familial Hypercholesterolemia is planned is Slovenia. Screening is based on total cholesterol levels and family history

of hypercholesterolemia and/or early cardiovascular disease; in particular, genetic screening is recommended when total cholesterol is over 230 mg/dL or over 190 mg/dL plus family history of hypercholesterolemia and/or cardiovascular disease before age of 50 years. In Italy, Familial Hypercholesterolemia still remains under-diagnosed and under-treated. If we consider that Italian population is around 60 million, we should expect 240,000 / 300,000 FH patients, while only 1% to date has received a diagnosis of FH. In particular, in Campania Region, we expect to have around 3500 children (0-14 years) affected by FH. Moreover, we have to consider that in Campania Region there is the highest percentage of obese children in Italy (23%) and this condition could create confusion between a diagnosis of hypercholesterolemia obesity-related and that genetically determinated.

Main achievements

Genetic diagnosis particularly useful in asymptomatic children allowing for the detection of definite FH patients. Furthermore, defining their genetic status maybe of considerable importances the compound heterozygous status is much more severe than the heterozygous one. We tried to characterize the genetic background of 164 Italian children with clinical suspect of FH and to correlate lipidprofile and genetic status. Patients with mutations in LDLR, APOB and/or PCSK9 gene (129/164) showed increased levels of LDL-Cholesterol and LDL/high-density lipoprotein (HDL) ratio and decreased levels of HDL-Cholesterol. The association of the LDL/HDL ratio with the presence of mutations was assessed independently of age, (body mass index) BMI, parental hypercholesterolemia, premature coronaryartery disease (CAD), triglycerides by multivariate logistic regression (odds ratio [OR] = 1.701 [1.103-2.621], p = 0.016). The LDL/HDL ratio gradually increased from patients without mutations to patients with missense mutations, null mutations and compound heterozygotes. The LDL/HDL ratio proved to be a better parameter than LDL-C to discriminate children with or without genetic alterations.

Future perspectives

1. Establish the prevalence of hypercholesterolemia in the pediatric population of the Campania Region, we propose a screening of the lipid profile (CT, LDL-col, HDL-col, TG) in children from the age of 5.

2. We propose to perform genetic analysis in children with LDL-cholesterol values above the 95° percentile and/or family history of early cardiovascular events (before 50 years of age). We could do a secondary prevention in these at risk children prescribing them the most appropriate dietary and / or therapeutic treatments needed as soon as possible.

Publications

1. *Di Taranto MD, de Falco R, Guardamagna O, Massini G, Giacobbe C, Auricchio R, Malamisura B, Proto M, Palma D, Greco L, Fortunato G. Lipidprofile and genetic status in a familial hypercholesterolemia pediatric population: exploring the LDL/HDL ratio. ClinChem Lab Med. 2019; doi:10.1515/cclm-2018-1037.*

External collaborations

- *Fortunato G, Department of Molecular Medicine and Medical Biotechnology, University Federico II, Naples, Italy. And CEINGE, Advanced Biotechnonology s.c.ar.l., Naples, Italy*
- *Guardamagna O, Department of Public Health and Pediatric Sciences, University of Turin, Italy*