

Genetic and epigenetic, the case of hypercholesterolemia

To size up how important the human genome description is, the researchers who described it illustrated the relevance of genes in the development of conditions that create a large burden on public health. The authors reported on ApoE genetic variations and their role in the development of hypercholesterolemia and cardiovascular disease. This is an important issue, which calls upon us to reflect on how knowledge has evolved in the past decades.

Morbidity and mortality from cardiovascular disease (CVD) across Europe between 1990 and 1992 was greatly dissimilar among countries. Mortality among 45-74-year-old men was 655/100 000 inhabitants per year in Scotland, whereas it was 142/100 000 inhabitants per year in France, i.e., 4.5 times higher. The mortality rate among Scottish women in the same age group was 7.5 times higher than among their French counterparts.¹

Subsequent studies showed that in Europe, based on a continuous gene pool, the rate of CVD varied over time due to environmental changes, which demonstrates the role of diet. Variations in the European diet, from North to South, started to account for numerous findings. Studies on the composition of adipose tissue indicated an increase in monounsaturated fatty acid intake in Southern countries, together with a reduction in saturated fat consumption. Therefore, the role of fats was studied, especially saturated fats, in addition to their relationship with CVD and the benefits of omega-3 and omega-6 fatty acids.^{2,3}

Apolipoprotein E (apoE) is one of the major components of very low-density lipoprotein (VLDL). ApoE plays an important role in lipoprotein metabolism and exists as three common isoforms: E2, E3, E4, coded by three alleles: apoE2, apoE3, apoE4, which are located on chromosome 19. The three isoforms have different functional properties: the apoE4 allele is associated with an increase in cholesterol and LDL-cholesterol levels, whereas the apoE2 allele is associated to the opposite.⁴

In Northern Europe, the United States and Canada (Caucasian populations), the prevalence of apoE4 is 13%-17%. In China, it is low (5%-7%), whereas in Africa it reaches 20%-30%. From the North of Europe (Finland) to the South (Greece), prevalence decreases from 18% to 8%.

The association between carriers of the apoE4 allele and high cholesterol levels is significant in the populations with a saturated fat- and cholesterol-rich diet. And it is weaker in the populations with a healthier lipid profile diet (e.g., the Mediterranean diet). This means that an atherogenic diet is necessary for the association to become evident.¹

Decades ago, thanks to the Argentine Infarction Prevention Program (*Programa de prevención del infarto en la Argentina*, PROPIA), it was possible to carry out a wide dissemination of the risks of hypercholesterolemia and the nutritional measures necessary to fight it. Marcelo Tavella, M.D., and his group implemented several interventions and issued publications, making them the pioneers in our country who warned on adult hypercholesterolemia and extended its prevention to the pediatric population. Apolipoproteins (specifically apoB) were studied in adult at-risk populations; in more recent years, Virginia Bañares, M.D., studied the prevalence of apoE4 carriers.⁵

In 2005, using a sample with a high prevalence of students with hypercholesterolemia, and then in 2009 through a successful experience with interventions, the Río Cuarto Group (Córdoba), led by Alberto Lubetkin, M.D., and J. A. Robledo, Biochemist, published an intervention implemented in students in *Archivos Argentinos de Pediatría*, and findings were very interesting.^{6,7}

Both Tavella and Robledo demonstrated that efforts paid off.

In 2015, the SAP's Committee on Nutrition published a consensus on the management of dyslipemias in pediatrics. It was an excellent study that introduced screening at 6 years old.⁸

However, in order to reduce the population risk, it is necessary for national and provincial top health authorities to implement continuous policies and showed their commitment. The third National Survey on Risk Factors (*Encuesta Nacional de Factores de Riesgo*, ENFR, conducted by the National Ministry of Health) showed that following the increase observed in the first and second surveys, the prevalence of hypercholesterolemia had reached a plateau.⁹

Based on the evidence, physical activity and a healthy diet help to reduce and prevent high cholesterol levels, regardless of the genetic

burden, highlighting once again the relevance of epigenetic factors. In this regard, the National Ministry of Health, via the Division of Health Promotion and Control of Noncommunicable Diseases, proposed a series of actions towards habit modifications, e.g., the Healthy Argentina Plan, the Cardiovascular Disease Prevention guideline, and the "Trans-fat-free Argentina 2014" campaign, which changed the Argentine Food Code and limited the amount of fat allowed in industrial food. Also on the part of the Ministry, via the REDES (Health Care Integrated Networks) program, the distribution of statins among primary care providers was implemented through the REMEDIAR program, aimed at subjects with specific indications. We should all stand up for the continuation of these policies, assess their impact, make the corresponding corrections, and fight against non-communicable chronic diseases. As described by the consensus of the European Atherosclerosis Society, familial hypercholesterolemia is scarcely diagnosed and treated.¹⁰

Once again Robledo et al. address the issue by opening a window to genetic aspects in this issue of *Archivos Argentinos de Pediatría* "Relationship between genetic and environmental factors and hypercholesterolemia in children" (page 419). Their results show the weight of the genetic burden estimated through positive family history in school children, that are stronger than other risk factors in this study. This type of reports are very important, because opens the way to further researches.

Nutrition, as applied to public health, should start considering how to use the information obtained from research in nutrition and genomics. A better understanding of genetic variations, risk factors, and sensitivity to therapeutic diets will probably have an impact, firstly on clinical nutrition, and secondly, on public health nutrition.

It would be desirable for pediatricians to become committed and show the results of interventions or studies that would allow us to know the genetic burden in our population,

spread the word on the importance of approaching this issue from as early as childhood, the window of opportunity for prevention in our life cycle. ■

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