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THE ROLE OF LIPOPROTEIN(A) IN CARDIOVASCULAR DISEASES IN CHILDREN AND ADOLESCENTS

Essay

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JEL Classification

I10, I13, I19

Abstract

Lipoprotein(a) is an independent and genetically predominant factor in determining cardiovascular diseases in children and adolescents, given that diet and lipid-lowering agents have no impact on Lp(a) serum levels.

Many studies in the literature highlight the atherogenic and prothrombotic potential of lipoprotein(a) in children with a family history of cardiovascular disease and hypercholesterolemia, causing coronary vascular disease, cerebral accident and peripheral arterial diseases. Given this potential, lipoprotein(a) dosage can be involved in the prevention and reduction of cardiovascular risk factors in childhood and adolescence, thus reducing morbidity and mortality.

Lipoprotein(a) is a dimer comprising a single LDL molecule and apolipoprotein B-100 linked to apolipoprotein A (APO [a]) (encoded by the APL gene) through a disulfide bond (Kronenberg et al., 2013). The clinical interest in lipoprotein(a) is due to its action as a cardiovascular risk factor. Even though it is not considered to be an independent risk factor, elevated levels of Lp (a) have been associated with cardiovascular diseases in many studies, revealing clear evidence of the interaction between Lp (a) and other cardiovascular risk factors (low-density lipoprotein cholesterol-LDL, high-density lipoprotein cholesterol-HDL and homocysteine).

Due to their complex structure, approximately 80% of the Apo(a) amino acids are homologous to those of plasminogen, suggesting that increased levels of Lp(a) could have both an atherogenic and prothrombotic effect, causing coronary vascular, cerebral and peripheral arterial diseases (Spence et al., 2010; Jones et al., 2007). Studying lipoprotein(a) serum concentrations in children is of utmost importance due to the fact that, unlike LDL, its concentration is stable throughout one's life. Lp(a) levels range from one individual to another and are not influenced by gender, age, rest, diet, lifestyle; the variability of serum levels being determined by the Apo(a) gene polymorphism caused by the variable number of KIV repeated at the level of the APL gene (Kronenberg et al., 2016). The clinical studies have shown that elevated concentrations of Lp(a) are associated with an increased risk of cardiovascular disease and represent an independent risk factor for the disease, even in the presence of normal cholesterol and triglyceride levels.

A family's medical history of cardiovascular diseases is an independent risk factor for assessing cardiovascular risk. It is carefully evaluated in the context of the potential lineal descendant diseases. Many of the studies in which the general paediatric population was included highlight the association between increased levels of Lp(a) and a family history of cardiovascular diseases. In a study conducted on 240 children with familial dyslipidaemia and a positive history of premature coronary arteriopathy, Dirisamer et al. found a >2-fold higher median Lp(a) level in comparison to children without such a family history (Dirisamer et al., 2008). In another study carried out by Guardamagna et al. on 231 patients with ages ranging between 2 and 18, Lp(a) and lipid fraction levels did not differ between the patients with a family history of cardiovascular diseases and those without. Nevertheless, the patients with such a family history (comprising three or more cardiovascular events) presented higher levels of Lp(a) (> 85 percentile) (Guardamagna et al., 2011).

This could be noticed in other two studies carried out by Saez de La Fuente et al. (Saez de La Fuente et al., 2006) and Obisesan et al. (Obisesan et al., 2004) in which the family history of cardiovascular diseases was significantly associated with increased Lp(a) levels. These results raise the attention of paediatricians, as well as of paediatric cardiologists to the early identification of individuals with high Lp(a) levels and to the effective intervention at lower levels of modifiable risk factors, such as LDL-cholesterol, thus reducing morbidity and mortality.

Obesity is a major risk factor for cardiovascular diseases, the body mass index, as well as other anthropometric measurements being correlated with lipid and lipoprotein metabolism in children and adolescents. Meabe et al. conducted research on a paediatric study group in order to highlight the fact that there is no connection between anthropometric variables and Lp(a) levels (patients with low weight or MBI, yet with increased Lp(a) levels were identified). Moreover, a positive correlation between Lp(a) and LDL-cholesterol, Lp(a) and total cholesterol, Lp(a) and Apo lipoprotein B was noticed, thus suggesting an association between Lp(a) levels and lipid profile (Meabe et al., 2006). According to Silva and Zurita (Silva et al., 2012), childhood obesity is a significant risk factor before the children grow up to be adults, due to the consequences related to dyslipidaemia, hyperinsulinemia, hypertension, autonomic dysfunction and severe psychological stress determined by social stigma.

The atherosclerotic process begins with endothelial dysfunction as early as childhood. Lipoprotein(a) interferes with the normal coagulation processes, stimulating the production of plasminogen activator inhibitor-1 (PAI-1), determining a reduced capacity of the tissue plasminogen activator (t-PA) to activate the dissolution of the clot. The increased production of PAI leads to proinflammatory events by activating monocytes adhesion to the vascular wall.

Lp(a) modulates platelet activation through the interaction of platelets with the collagen fibers exposed at the level of the affected vascular wall, leading to proatherosclerotic and prothrombotic phenomena. Cho and collaborators describe the manner in which the increased concentration of Lp(a) in parents increase the probability of developing early cardiovascular diseases in children, through the action of apolipoproteins in mediating endothelial cell dysfunction (Cho et al., 2008). Sorensen and collaborators carried out a study on 30 children with familial hypercholesterolemia and 30 healthy 7 year old controls, whose femoral artery functionality and

integrity was investigated. They discovered a degree of reduction of the endothelial function in children with a history of hypercholesterolemia, as well as higher levels of lipoprotein(a) compared to the controls. Due to the fact that the level of lipoprotein(a) is constant during childhood, its values are predictive of their clinical evolution (Sorensen et al.,1994).

Jouni Lapinleimu et al. selected a control group and a group with family hypercholesterolemia (each group being represented by 7 month-old children and their families) who received individualized dietary recommendations so as to reduce total cholesterol concentration throughout the period of the study. Lp(a) and cholesterol were repeatedly measured during the study. Seven year old children were recruited for brachial arteries ultrasound and lipid profile assessment. In cases with increased family Lp(a), associated with an appropriate diet and lifestyle, an attenuation of endothelial lesions was demonstrated; this association can be established through the physician's intervention and the collaboration with patients in establishing an early management for the purpose of preventing cardiovascular diseases (Jouni et al., 2015).

The National Heart Lung and Blood Institute and American Academy of Paediatrics recommend routine cholesterol screening for children aged between 9-11 and 17-21 years old. The 9-11 age interval was chosen in order to identify stable lipid levels before puberty.

Screening is performed in order to prevent and reduce cardiovascular and cerebral diseases, due to the fact that many studies identified high levels of lipid profile, as well as the presence of aortic atherosclerosis in young children. The experts on the risk factors involved in ischemic vascular disease in children are unsure about the clinical utility and involvement of cholesterol in this pathology in the paediatric population. The literature provides little data to explain the role of dyslipidaemia in ischemic vascular diseases in children. Dyslipidaemia has a greater impact before puberty and during adolescence (Skinner et al., 2012) (when cholesterol levels are higher) and can be a risk factor for ischemic vascular diseases through the coexistence of an inflammatory process.

In a study conducted on a paediatric population diagnosed with cerebral accidents (28 days - 18 years old), Sally Sultan et. al aimed at identifying lipid involvement in the cerebral accident mechanism in children and adolescents. Therefore, in the study group chosen, total cholesterol, LDL-cholesterol and Lp(a) values were analysed. The incidence of cerebral accidents associated with

increased Lp(a) levels was identified, on average, at the age of 6 years old; there was also a pre-adolescent pick (7-12 years old). The lipid profile (older children-adolescents with recurrent cardiovascular diseases) was investigated in only a quarter of the group selected, establishing a correlation of the role of Lp(a) and cholesterol as a risk factor in the occurrence of cardiovascular diseases in children (Sultan et al., 2014).

The association between Lp(a) and cardiovascular risk factors was studied by many international groups, leading to a more reliable and appropriate panorama of the population, especially among children and adolescents at this age group, Lp(a) being a potential predictor of cardiovascular risk. Given this potential, it can be stated that lipoprotein(a) dosage could be involved in preventing and reducing cardiovascular risk factors in childhood and adolescence, thereby reducing morbidity and mortality. Nonetheless, implementing programmes aimed at changing the lifestyle of the risk factors, making the association with individual choices in adopting and maintaining healthy habits, cultivating a cultural appreciation of health is an extremely important instrument in achieving healthy lifestyle goals and objectives.

Dyslipidaemia in the paediatric population contributes to early atherosclerosis and cardiovascular diseases. Hypercholesterolemia screening during childhood is traditionally performed only in a certain group of children with a history of familial hypercholesterolemia. Nevertheless, the group of experts in cardiovascular health and cardiovascular risk reduction in children and adolescents has established the fact that the early identification and control of dyslipidaemia in childhood would substantially reduce the risk of cardiovascular diseases in adulthood.

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