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ARE FETAL AND EARLY NEONATAL PERIOD DEFINING OUR LIFE DESTINY?

Introduction

Children born small for gestational age (SGA) represent one of the most important public health and population problem of every modern country: both in its frequency and in its high and early morbidity and consequent mortality. SGA infants are classified as those whose birth weight and/or birth length deviates more than 2 SD below the average for gestational age. An estimated prevalence to date is more than 10% (1). These children suffer from 2 problems: 10% of them have inadequate growth hormone secretion and thus remain permanently low stature if not treated with growth hormone after the second year of life. About 90% of children who make a rapid growth phenomenon are at high risk of developing serious metabolic disorders by the process of foetal and early neonatal programming. As a result, sudden addition in body weight is enabling early constitution of the metabolic syndrome with all its consequences, including high early cardiovascular and cerebrovascular morbidity and mortality.

Disease programming

Programming implies stimulus or insult during critically and particularly sensitive period of development. It has a lifelong repercussion on the organism and for which the organism has a predictable adaptive response. Any structural or functional changes that occur in this way are generally irreversible. The period between the effect of the environmental factors and the occurrence of the disease can last long, even for decades… Foetal environment, gestational length and weight could have crucial effect on physical and mental health even in adulthood (2).

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Pancreatic beta-cells change

In utero under nutrition definitively and permanently changes the phenotype of beta-cells – insufficient microvasculature decreases number of beta-cells and makes them susceptible to oxidative stress. In this environment the total number of beta-cells is reduced for 40% at 21st day of foetal life. Foetal beta-cells developed in the nutritive withdrawal will never be able to respond adequately to higher metabolic requirements or any oxidative stress.

Due to impaired beta-cells, the levels of antinflammatory adiponectin have been reduced while levels of resistin have been increased. This favours inflammation and oxidative stress, and consequently, the occurrence of insulin resistance and type 2 diabetes. The programming of subsequent metabolic sequences is often based on insulin resistance. There are many explanations of the constitution of insulin resistance as a protective sign of intrauterine malnutrition - unequivocally there is a direct negative correlation between birth weight and glucose intolerance, i.e. insulin resistance (3). With the time, the organism adapts to a lower insulin production from insufficient insula by increasing the number of insulin receptors in insulin tissues, which *de facto* constitutes the basis of insulin resistance.

Kidney

The changes may also affect organs not directly involved in the establishment of insulin resistance but can significantly participate in the pathogenesis of the metabolic syndrome. Thus, it has been shown that endangered foetuses have a lower number of nephrons and an inadequate renal function. The reasons for insufficient nephrogenesis are numerous: from inadequate intra renal RAA system, which is a key factor of normal nephrogenesis, through reduced activity of the antiapoptotic homeobox gene Pax-2 to increased sodium transport in distal tubules likely caused by the intensification of oxidative stress in these circumstances (4). Later inadequate renal function may be responsible for the onset of hypertension.

Heart

The heart consists of a few numbers of cardiomyocytes with a larger diameter. Consequently, it is much more sensitive to infarction during the ischemic period and reperfusion in adulthood. Early-installed increased pressure stimulates poor quality cardiomyocytes to prematurely abandon the normal differentiation cycle and quickly undergo hypertrophy. Chronic foetal anaemia causes remodelling of the coronary tree and so altered persists until the adult age. The thickness of intima media in the

posterior wall of the common carotid artery, which is an excellent non-invasive marker of generalized atherosclerosis, has been greatly increased in the first few years in children born SGA (5). This confirms that the programming of atherosclerosis, coronary disease and myocardial infarction occurs in the first weeks of life, and that cardiac interventions 50 years after the programming of such diseases are an essential expression of the weakness of modern medicine, and thus in no way proof of its triumphal progress and expertise.

Gonads

Children born SGA may have a variety of reproductive problems, which are due to the disrupted responsiveness of the hypothalamus-pituitary-gonadal axis and hyperandrogenemia to which they are prone. Namely, insulin resistance leads to increased production of androgen in a several ways - a significant number of adolescents with polycystic ovary syndrome (PCOs) are currently recruited in the SGA group (6).

Central nervous system

Foetal malnutrition is also reflected on cognitive functions. So 49% of adults born as SGA have lower school performance or lower intelligence quotient than those born with adequate birth weight or length (7). Namely, the intrauterine growth retardation is associated with a number of neurodevelopmental consequences, such as lower intelligence, poorer academic performance, social incompetence or behavioural problems, and even symptoms of psychiatric disorders in early adulthood - all the way to suicide.

Liver

Due to the effect of insulin, synthesis of endothelin 1 in the liver has been increased. Endothelin 1, as the dominant vasoconstrictive molecule, increases the risk of atherosclerosis, hypertension and myocardial infarction (8). Metabolic programming includes the liver, which consists of smaller hepatic lobes with larger dimensions.

Early postnatal overeating

As a nutritional restriction in the early foetal period, overeating in the early neonatal period also results in irreversible changes both on organic systems and tissues, as well as on the genome, mainly through various epigenetic changes. Children born

SGA, which have grown up suddenly with an addition in body weight, already in the first year of life have reduced insulin sensitivity and increased insulin resistance, with the consequent development of central, abdominal obesity. Various factors contribute to the development of obesity in that age. Reduced density and volume of neurons, above all melanocortins, which are well-known centres of satiety, and consequent domination of centres of hunger in the supraoptical nucleus - the neuropeptide Y, have been demonstrated in undernourished foetuses and neonates (9). This permanently changes the appetite and habits of the undernourished foetuses, making them the people with a great appetite until the end of their life, i.e. always hungry people.

When the adipocytes are filled with triglycerides, the secretion of leptin increases in an attempt to prevent lipid deposition in non-adipose tissues: skeletal muscle, liver, myocardium, or beta-cells. In obesity, the functional lack of leptin will lead to generalized steatosis, lipotoxicity, and lipoapoptosis. Lipotoxicity of beta-cells, myocardial or skeletal muscles leads to type 2 diabetes, cardiomyopathy and insulin resistance, or to the 21st century monster - the metabolic syndrome.

Therapy

Children born SGA are a major problem because of their high incidence and morbidity as well as the early mortality they carry. In an attempt to prevent numerous cardiovascular, cerebrovascular and metabolic consequences of the birth of SGA infants, it is necessary: 1) to improve the whole range of legal, social, economic and other prerequisites in order to better protect pregnant women and decrease incidence of SGA child births; 2) to involve supplementation of taurine and other necessary micro nutrients as early as possible in all pregnant women in whom intrauterine growth retardation is found; 3) to make a systematic and comprehensive detection and adequate monitoring of all children born SGA; 4) to insist on natural nutrition in all SGA infants, because this is certainly the best way to correct the wrong programming of a complex neuroendocrine network that otherwise rapidly leads to the onset of metabolic and cardiovascular diseases; 5) after a breastfeeding period, to insist on proper and balanced nutrition and the regular physical activity of children born SGA; and 6) in the younger age, to seek for markers of the metabolic syndrome and early indicators of cardiovascular and cerebrovascular disease.

Our experience

In Serbia, for a long time, about 65,000 children are born annually. According to a respectable database (“IOS database”) of children treated with growth hormone, in our country during period of 9 years were born about 590,000 children. This would

mean that during this period about 10% of them were SGA (1), hence 59,000 of them. If 10% of such children never make a catch-up growth phenomenon and need to start supplementation with a growth hormone early, it means that throughout the duration of this database (9 years), 5,900 of them should receive a growth hormone. However, only 260 children who receive growth hormone are in the database – thus only 4% of them are detected. More tragically – none of SGA children with rapid postnatal growth, programmed for adult illness, has been recognized up to this day!

Conclusion

The low level of recognition of SGA entity represents a major contemporary problem everywhere in the world, even in our country (Table 1). Regarding the clear and high consequences that this syndrome carries with them, the problem of poor recognition of children born SGA in Serbia is imposed currently as the most important public health and population problem.

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