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Editorial

METABOLIC SYNDROME—ESSENTIALLY A BRAIN DISEASE

Modern industrialization in respect of food production has resulted in many choices of calorie-abundant easily available food with little physical efforts in comparison to earlier days when human species had to exert enormous effort to gather food. But this overcorrection of food availability ushered in deleterious health problems of overnutrition. From the physiologic point of view, these health issues are often preceded by a cluster of pathological features like central obesity, impaired glucose tolerance, insulin resistance, dyslipidemia, high blood pressure and these all are collectively known as metabolic syndrome (MetS). The indicators or the risk factors of MetS like hypertension, adverse lipid profile, central obesity and impaired glucose tolerance tend to be clustered in children and adolescents with unhealthy lifestyles and diets rich in excessive cholesterols, saturated fats and salts along with low consumption of dietary fiber that too in presence of sedentary habit and increased television viewing (joint WHO/FAO Expert consultation 2003; WHO 2005). Various names are given to this entity—to mention a few insulin resistance syndrome, CHAOS (coronary artery disease, hypertension, atherosclerosis, obesity, and stroke), civilization syndrome, new-world syndrome, syndrome X, and finally, MetS.

Metabolic syndrome is now called a global epidemic. About one-third of urban population in large cities of India is affected with MetS. Community-based study from eastern India prevalence of MetS is 31.4% and more common in females (48%) compared to males (16%). Rural prevalence is reasonably low (9.3%).

WHO Clinical Criteria for the Diagnosis of Metabolic Syndrome

Diagnosis of MetS depends on impaired glucose tolerance or diabetes and/or insulin resistance, together with two or more of the following components:

- Raised arterial pressure >140/90 mm of Hg.
- Raised plasma triglycerides >1.7 mmol/L or 150 mg/dL and or low HDL cholesterol <0.9 mmol/L or 35 mg/dL in men and <1 mmol/L or 39 mg/dL in women.
- Central obesity (males waist to hip ratio >0.9; females waist to hip ratio >0.85 and or BMI >30 kg/m^2
- Microalbuminuria (urinary albumin excretion rate >20 g/min or ACR >30 mg/g).

Recent research has pointed out a strong association between pathogenesis of MetS and brain dysfunction. Dietary omega-3 fatty acid deficiency increases vulnerability to metabolic dysfunction. The docosahexaenoic acid (DHA) derived from omega-3 fatty acid is a structural component of brain plasma membranes and crucial for neuronal signaling but brain is incapable of synthesizing DHA. This may be reflected in dysfunction of hippocampus, and hypothalamic arcuate nuclei. The two hypothalamic neurons pro-opiomelanocortin (POMC) neurons which inhibit feeding (anorectic) and neuropeptide-Y (NPY) neuron which stimulate feeding (orexigenic) are affected in absence of DHA. These two nuclei predominantly located in the arcuate nucleus of hypothalamus project to parts of brain which modulates functions such as autonomic function, wakefulness and learning. A tilt in this anorectic–orexigenic pathway or balance leads to obesity. This is also perhaps genetically determined. Omega-3 fatty acid deficiency also disrupts insulin signaling pathways as evidenced by changes in insulin receptor and insulin receptor substrate.

Brain Autophagy

Lysosomal degradation pathway plays an essential role in maintaining cellular homeostasis. Cell survival, growth and differentiation against adverse conditions collectively through evolutionally conserved lysosomal degradation pathway are known as autophagy. Intact autophagy is required for hypothalamus to control metabolic homeostasis. Hypothalamic autophagy defect is responsible for development of insulin resistance, obesity and other components of MetS. Secondly, this autophagy defect in the CNS is linked to a number of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease and also cerebrovascular diseases. In addition, overnutrition-induced central metabolic dysregulations also play a role in hypothalamic inflammatory aspects of MetS. Most hypothalamic neurons express toll like receptor (TLR) and can mediate innate immune response to local and systemic inflammation. In the context of MetS, excess saturated fatty acids produce an inflammatory response predominantly through activation of TLR signaling in hypothalamus. In the past decade,

research indicates MetS results from innate activation of immune system in response to overnutrition. This type of inflammation exists in different tissues but CNS is the primary site for induction of MetS by nutritional inflammation.

Impact of Metabolic Syndrome on Brain

Impaired cerebrovascular reactivity, increased carotid stiffness (increased intima/media thickness) — may be reflected in increased white matter changes seen in adults with MetS and are therefore likely vascular in origin. Endothelial dysfunction leads to subclinical ischemic brain damage; silent brain infarction together with widespread amyloid deposition plays key role in the development of cognitive impairment and dementia.

Prevention of MetS requires multipronged approach which includes behavior modification, dietary modification (more fruits and vegetables, less fried foods to cut down trans-fat), and prevention of smoking and alcohol excess. Regular exercise needs to be promoted both by individual and community intervention.

Therefore, in conclusion, MetS starts in brain hypothalamus and ultimately its effect on brain by producing cognitive decline, ischemic cerebrovascular disease and neurodegeneration. Hence MetS is rightly called a disease of brain.

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