NEUROMETABOLIC DISORDERS

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The study of the nervous system, brain being the major component, is in the forefront of human endeavor in modern biology and medicine. Brain function is mediated through a complex anatomical (neurons and glia) and functional (neurotransmitters/hormones) network comprising a series of extra cellular and intracellular messengers. The motor and cognitive functions of the brain are regulated through electrochemical signal transduction involving the synthesis, release and postsynaptic interaction of neurotransmitters with corresponding receptors. Considering its overall importance in the survival of the living being, nature has provided the human brain with both anatomical (buoyancy of CSF compartment, meninges and skull) and functional (blood brain barrier; BBB) protection against insults (mechanical or biochemical) that are detrimental to its function. Nevertheless, the function of adult brain could as well be affected by exposure to certain toxins, substances of abuses, heavy metals, chemicals and infection. Additionally, the brain function could as well be adversely affected by higher level of certain intermediate metabolites such as ammonia etc., that are synthesized and excreted by peripheral organs. Incidentally, human brain is most susceptible for insults such as infection and inborn metabolic errors (IEM), during the early period of its growth and development, which extends up to couple of years of postnatal period. Diagnosis of IEMs during early neonatal period, before the clinical presentations, helps in protecting the developing brain against toxic effects and reduces the risk of living with severe morbidity or certain death during neonatal period.

The biochemical composition of brain, distinctly different from other organs, there exists a very complex relationship between the concentration of metabolites and the neural function. The

concentration of intermediate metabolites in general, the neurotransmitters in particular, are subjected to change with age, environment (both external and internal milieu) stress level, circadian rhythms, diet, medications / substances of abuse and the functional status of gastrointestinal / hepatobiliary systems. The brain function, including the autonomic nervous system, can be adversely affected by malfunctioning of peripheral organs such as liver, kidney etc., including the accumulation of neuroactive substances that are of endogenous or exogenous (like toxins) origin.

Brain consumes between a quarter and a third of the body's total oxygen consumption and glucose implying the production of highest rate of reactive oxygen species wherein glucose is converted to high energy intermediates like ATP and NADPH via Krebs' cycle in mitochondria through the electron transport chain. In view of neural and muscle tissues requiring a great deal of energy through oxidative metabolism they are vulnerable to oxidative stress. Since brain is relatively deficient in oxidative defense mechanisms it is at great risk of damage mediated by reactive oxygen species (1). Some of the common mitochondrial disorders which affect the brain function are Kearn-Sayre syndrome, Myoclonic epilepsy with ragged red fibers (MERRF) & Mitochondrial encephalomyopathy lactic acidosis and stroke like episodes (MELAS). Apart from the direct effect of some of the substances of abuse on brain, chronic ethanol ingestion elicits oxidative stress in brain as evidenced by the reported increase in thiobarbituric acid reactive substance associated with decrease in glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase level in the brain (2). Hence substances/metabolites, such as ascorbate (vitamin C), tocopherol (Vitamin E), carotenoids, bioflavonoids and Co-enzyme Q 10 etc., may prove to be useful in reducing the deleterious effects of reactive oxygen species.

Many of the endogenous metabolites, in the event of their being not detoxified and excreted tend to increase in circulation and turn out to be neurotoxic as in case of inborn errors of metabolism. Further, liver being one of the main organs

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involved in detoxification process and being endowed with cytochrome P 450 (3) has an important role in the metabolism of several substances including xenobiotics. The ability of liver to detoxify various substances depend upon its enzymatic activity and if fails to function as seen in hyperammonemic syndromes and porphyrias subjects will present with neurological deficits and encephalopathy. In born errors of metabolism which affect urea cycle are amongst important causes of hyperammonemia in children but in adults various acquired causes like liver injury, urinary tract infections (4) drug therapy specially with valproate (5) can lead to hyperammonemia. Porphyria's, in particular hepatic porphyrias present with neurological symptoms while that of erythropoietic porphyrias are hematological in character(6).

Even an overtly active detoxification system due to abundance of toxic substances in the circulation the liver has to detoxify, enhances oxidative stress, which manifests in turn affect oxygen sensitive tissues such as brain. Apart from disturbances in intermediate metabolism affecting the brain function, neurological diseases also result from protein misfolding (7) such as Alzheimer's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Spino cerebellar ataxia etc. The hallmark event in these diseases is the accumulation of misfolded proteins which aggregates in various cells leading to cell death and ultimately organ dysfunction. Changes in the receptor / ion channels expression also result in malfunctioning of brain e.g., changes in the chloride transporter expression, by reducing or even reversing the inhibitory influence of GABA has been attributed to generation of seizures acutely or leads to the process of epileptogenesis (8).

Better understanding of brain function in coming years will open new avenues in the treatment of neurological disorders.

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