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Neurodegenerative Diseases Current Research

Neurodegenerative disorder: Five groups of Questions to address. Routes to Therapy

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The disease burden of neurodegenerative disorders in ageing population is alarming and is considered a new epidemic of pandemic nature. A doable new approach is probably required to investigate its pathogenesis from Virchow's point of view that disease has its origin inside the cell, and consequently follows what therapeutic procedure is to pursue. Here, the cells of concern are hundred billion neurons of the brain which have two important properties; polarity of their cell membrane and serenity of their genes. The membrane polarization of cortical neurons is best suited for signal-information transformation in the tripartite neuro-neuronal-astrocyte synapses in the cerebral cortex. Neurons also have too little activity on mitotic fronts throughout their life and therefore, the genes of neuron maintain the original serenity of DNA strands coiling around the large spherical protein, histone. Because of such integrity of neuron as a cell, its microtubular machinery is extremely stable. Microtubles are involved in information channeling from cell membrane to strategically spatio-temporally dispersed autonomous cellular organelles, such as nucleus, mitochondria, lysosome and Golgi apparatus and vice versa. Unlike cytosolic route of molecular signaling, which is slow and discrete for a specific organelle, microtubular pathway could be considered an information highway for fast dynamic information exchange between the cell membrane and all other organelle together. It is this microtubular machinery which gets unsettled during apoptosis of neurons and crumbled in neurodegenerative disorders.

Like any other cell, neurons could go through metabolic stress (e.g., imbalance of aerobic, anaerobic utilization of glucose and Warburg effect), oxidative stress (e.g., free radical injury), endoplasmic reticular stress (e.g., protein mis-folding against the logistic support of different cognitive function), genotoxic stress and finally apoptotic stress. Imbalance between relative resistance of neurons to senescence, telomerase activity, repair of broken chromosome at the telomere ends and P-53 activity could push the neuron and/or supporting glia towards apoptosis. Imagine the situation when even a fraction of cortical neurons and astrocytes in the cerebral cortex are under any of those five kinds of stress of certain magnitude for a considerable duration of time, and its consequence as cellular degeneration! Astrocyte degeneration often precedes or accompanies neuronal degeneration. The stress of protein misfolding is more observable in case of oligodendroglia and in myelin degeneration. Therefore, besides genetic predisposition to neuro degeneration, some new approach in investigation of neurodegenerative disorder is to be considered following five groups of research questions.

1.What consistent cognitive behavior the patient had had prior to his/her developing neurodegenerative disorder? Special attention is to be paid on three habits; physical

exercise, quality of sleep and cognitive play habits. Stretching exercise induces osteoblasts to secrete osteocalcin hormone which has growth promoting and soothing effect on neurons [1]. Tau protein (a misfolded protein) level of interstitial brain fluid and of cerebrospinal fluid have been related to sleep-wakefulness cycle [2]. Playing with, and teaching grand children has a preventive effect on neuro-degeneration. The same is true for attitude of learning new things while ageing. Besides, had there been exposure to neurotoxic substance (for example, mercury or lead) even in small dose but for a prolonged period? Were there any other specific environmental factors (for example, pollutants in passive smoking environment)?

2. For how long period, the patient had been undergoing such cognitive behavioral/environmental stress? Was the period uniform or punctuated by episode of infection (pneumonia, sepsis etc.), surgical intervention (which, like infection, could elicit cytokine storm), psychological trauma (separation or death of a near one), development of malignancy or deranged general metabolism which could alter Warburg effect on neurons! The brain is usually on fire during and following cytokine storm [3]!

3.What could be the characteristic of cellular stress in such situation? Is it endoplasmic reticular stress, oxidative stress, metabolic stress, genotoxic stress or apoptotic stress? Low grade neuroinflammation induces oxidative stress in mitochondria of neurons in the substantia nigra (Parkinson's disease). Does any other organ of the body show such visible stress effect? Is there any systemic manifestation of five kinds of cellular stress?

4. What is the magnitude of such stress in objective measurable scale, both at the level of behavior and at the level of cellular function? How much fraction of brain cells (neurons/glia) have probably been suffering from such stress?

5. If it is possible to pinpoint the kind of organelle stress, how does it take shape to result in disability through the common final pathway of intracellular information channeling by microtubular machinery?

We are aware of two histopathological hallmarks of Alzheimer's disease. One is the result of stress of misfolding of protein and formation of amyloid plaque which is deposited in extra-cellular matrix. The other is crumbling of cytoskeleton inside the neuron and formation of characteristic neurofibrillary tangle.

The first two of the above five questions are clinical and are for addressing the complex behavioral issue in terms of its nature, duration and may be the chronology of events with punctuations. Next two questions are hammering on kind of stress at the cellular level and their organ specific or systemic manifestation. The last question is to address the final cellular mechanism. There could be permutation and combinations of factors and therefore, different subset of questions might be framed accordingly to handle the tasks.

The bottom line in cognitive dysfunction is brain's inability of deft handling of different neuronal signals and converting the signal into information and vice versa. What could be that supra-cellular, supra-molecular, presently non-observable but informed operation, which switches on the cascading ladder of cognition [4] from conversion of signal into information, development of knowledge from information, transformation of knowledge into experience and sublimation of experience into wisdom? How the energy consumed in such cognitive processes, which remains invisible and therefore comes under dark energy of the brain, could be related to visible use of energy in terms of oxygen consumption and formation and utilization of ATP? The brain constitutes 2% of body weight but consumes 20% of total energy required for the body, which cannot be accounted by merely signaling activity. In all probabilities cognitive processes consume visible energy and transform this into invisible dark energy.

Once we become clear of the homeostasis of dark energy and visible energy in the brain, inside the neuron and glial cell in the context of neurodegeneration, we could take the therapeutic route towards metabolic and cell signaling pathway. There is another life-style route in therapy. There is no ailment or disease for the systems Whole. The brain within the cosmic Whole remains in its natural state. Degeneration is likely to follow disconnection of the brain from this Whole. In this context, therapeutic use of information holograph could be tried by willful reconnection of the brain in obedience, with the information holograph [5] through the waves of a melody on love and/or devotion, or melodious chanting of *Shloka*, *Mantra*. There is another objective way of getting the similar effect which depends on advancement of applied neutrino physics, since neutrinos are essential part of the Information-whole! Objective use of specifically focused neutrino-beam on and through the brain, could probably prevent neurodegeneration and restore it to its normal state. The research question is, could tau-neutrino eliminate tau-protein of the brain in tau-pathy neurodegeneration? Twenty first century is meant for technology development in responding effectively to such question!

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