New Hopes and Challenges for Treatment of Neurodegenerative Disorders: Great Opportunities for Young Neuroscientists

Neurodegeneration is a collective term used to describe the death of neurons in central nervous system diseases like Alzheimer's, Parkinson's, Huntington's disorders and amyotrophic lateral sclerosis (ALS). In this editorial, I provide a short overview of past, current and future of two examples of neurodegenerative diseases (AD and ALS) in research and therapies. There are several common elements (pathologies and pathways) that are shared in the neurodegenerative diseases, and the most prominent common element is the death of neurons that are in cortical and hippocampal regions in AD, in striatal regions in PD and in cortical and striatal regions (medium spiny neurons) in HD. In the case of ALS, motor neurons in the spinal cord and motor cortex area are degenerating. The mechanistic common element in the neurodegenerative diseases encompass multiple pathways, such as protein mis-folding, aggregation, inclusion body formation (Amyloid plaque, fibrillary tangles, lewy body, polyglutamine aggregates) and, oxidative stress, neuroinflammation and mitochondrial dysfunction.

Over the last few decades, intense research on the multiple fronts advanced our understanding of neurodegenerative diseases. Genetics and mechanism of neuronal pathogenesis contributed greatly and has created a wealth of knowledge and became the bases for novel technologies and multiple therapeutic targets for these neurodegenerative diseases.

Alzheimer's disease (AD) is the most prevalent and the number of people diagnosed with AD is exponentially increasing since Dr. Alois Alzheimer discovered it in 1907. AD is defined as an age-related phenomenon and how the cortical neurons die in the brain of AD patients remains poorly understood. Currently there are around 35 million people with AD in the world and is predicted to increase to 115 million in 2050. This will have important implications for Iran too as for the rest of the world. Developing countries like Iran will experience significantly bigger problem since Iran's young population of today (around 30 million) will be at 65 or higher by 2050. All neurodegenerative diseases are clinically unmanageable now and it is going to get worse as the aging population is increasing worldwide. It can be estimated that about one million people in Iran are suffering from Dementia at this time and nearly 70% of them would have AD. Since almost half of the population in Iran is around 25-30 years old now, then we can extrapolate that the number of people with dementia may increase to 10 million by 2050, where 70% or more will have AD. The problem will be enormously big to manage, as the number of people with AD in Iran could reach 5-8 million, if not more. Is there any plan to manage this problem? What should every one of us do now to assist in building up effective programs in managing the patients with dementia and AD from now on?

Although there is no drug to reverse the degeneration of striatal neurons in Parkinson's disease, there are some treatment options that are effective in treating the symptoms of PD, whereas treatment options for AD has little or no significant effect on the symptoms or the progression of disease. ALS and HD still have no treatment options. The data from research that has been reported over the past two decades guide the direction(s) for the future research in neurodegenerative diseases. The "failed clinical trials" in AD and other neurodegenerative diseases are lessons learned and can be used as platforms to lunch new research with revised hypotheses.

Current approved treatments against AD utilize two strategies; **a)** symptomatic treatment and **b)** disease modifying treatment. Anti-cholinestrase inhibitors are used as symptomatic treatment, while antioxidants and anti-inflammatory agents are used for disease modifying treatment. All the current treatments offered to patients with AD are merely palliative and appear to help temporarily in slowing the cognitive decline in AD patients. The effects of these treatments are at best marginal and they are prescribed since there isn't anything better to use to fight against AD. Clinical trials are ongoing and the search for effective drug(s) against AD being pursued worldwide.

New hope was spread in the communities for immunotherapy for AD using antibodies against Abeta plaques and some antibodies against fibrillary tangles. Active and passive immunotherapies have been tried in animal models of AD with reasonable success and currently being tested in humans. The side effects of these

antibodies are also the biggest concern and represent a big challenge for drug companies. The side effects are mainly attributed to adjuvants and autoreactive T cells, microhemorrages, aseptic meningioencephalitis, vasogenic edema. The most recent clinical trials on AD have been on anti-amyloid produced by several pharmaceutical companies. Unfortunately, some of them failed already. Bapineuzumab, an antibody against Tau that causes fibrillary tangles was tested by Pfizer and they reported the clinical outcome of their trial that it was found that bapineuzumab has no benefit to mental function in people with mild to moderate AD. Eli Lilly's anti-Abeta (Solanezumab) failed to improve cognition in AD patients in a phase III clinical trial. Genentech as subsidiary of Roche, is continuing clinical trial in AD patients using Crenezumab which is a humanized monoclonal antibody designed to bind to amyloid beta. The result from the clinical trials on this antibody is pending and will provide crucial direction in immunotherapy against AD. Antibody testing against Abeta is the ultimate test to determine whether Abeta (a major component of plaques) is the true toxic agent to cause AD, as the hypothesis has not been proven before. The question is what will happen if this hypothesis doesn't prove correct? What if other toxic agents are acting more profoundly in the cause of the neuronal death? No one knows the answer to this question and it might turn out that one may need to block the toxicity of multiple agents to prevent or delay the death of neurons. There are other avenues for therapeutic being explored. For example, metal homeostasis proposed to be a novel target for therapeutic strategy against AD, as metal dishomeostasis is linked to synaptic dysfunction, a novel mechanism for Abeta oligomers toxicity in AD. Early phase of clinical trials on metal regulating drug called PBT2 (derivative of Clioquinol, anti-microbial agent used in the 1960s) being developed by Prana Biotechnology, which is very promising.

New Hope for Motor Neuron Disease or ALS

Motor neuron disease or ALS is rare (2-5 in 100,000) but a horrifying disease that affects the motor systems leading to frank muscle weakness, muscle atrophy and full paralysis of voluntary muscle that results in death. Motor neurons are the most special neurons in the central nervous system. While they are very resilient, they are also vulnerable. These neurons die in motor neuron disease with pathologies that are very different to others, and on the other hand there are pathologies that are very similar to AD, PD and HD. There are three most common pathologies found in these diseases are; 1) oxidative damage, 2) neuroinflammation and 3) mitochondrial dysfunction.

The mechanisms of neuronal degeneration in all the cases are complex and involve multiple cascading pathways. Researchers have been partially successful to target one molecule at a time and block one pathway at a time in the laboratory models. These strategies haven't produced any success in humans yet. In the case of ALS, numerous successes were demonstrated in the laboratory models in the past two decades, but they all utterly failed in human trials. Everyone is trying very hard to find some clues into this. The hope will come from the new knowledge that reveals the exact nature of neuronal death in motor neuron disease. At this stage, the etiology of most of these diseases and the exact nature of neuronal cell death are not known and the pathological processes are poorly understood. The challenge is that what is causing the neurons to die and how? The good news is that, due to discoveries and genetic advancements in the past 20 years, the next 5-10 years will bring major breakthroughs. These breakthroughs will be the new hopes for therapeutic development.

Researchers (neuroscientists and neurologists) around the world and especially in Iran have their greatest opportunities to join in and discover the unknowns in the death of neurons in any of the neurodegenerative diseases. Why? Because the foundation is set and the platform has been built. Furthermore, the product of research done over the last two decades can be combined with technological advancements to discover the unknowns and develop novel and efficacious therapeutic strategies against neurodegenerative disorders.

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