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The Coming Dementia Pandemic: Prescription for a Cure

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We are barely emerging from the lingering COVID-19 pandemic that we are increasingly concerned with the coming of age of the dementia pandemic. Prompted by increasing lifespan following economic development, dementia in its multiple types has surfaced as a major global public health concern that may devastate world's economies and health care systems. Using 2015 as a baseline year with 46 million cases of dementia, the World Health Organization has predicted that number to jump to 82 millions in 2030 (an increase of ~ 78%) and to 152 millions in 2050 (an increase of ~ 230%). The number of cases augments significantly with age and the more so for people living in low- and middle-income countries (nearly 60% of people affected), where the sharpest rises in numbers are predicted. In 2013, the number of deaths was about 1.7 million (up from 0.8 million in 1990), but they are increasing significantly with age. While smaller than the number of deaths reported for the COVID-19 pandemic, they are steadily accelerating and may unfortunately approach (if not exceed) them.

On Dementia

Dementia is not an emerging problem as it has been with us since Antiquity. It was uncommon in pre-industrial times and relatively rare before the 20th century. 19th century physicians believed that dementia in the elderly was the result of cerebral atherosclerosis (either blockages of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex). Until the end of the 19th century, dementia was a much broader clinical concept that encompassed mental illness and any type of psychosocial incapacity. A turning point occurred in 1907, when Alzheimer's disease was described and associated with particular microscopic changes in the brain. It was seen as a rare disease of middle age. By the 1960s, the link between neurodegenerative diseases and age-related cognitive decline was established. By the 1970s, the medical community maintained that Alzheimer 's disease was the cause of the vast majority of mental impairments rather than just vascular disease, which is rarer than previously thought. In 1976, neurologist Robert Katzmann suggested a link between senile dementia and Alzheimer's disease dementia. By the end of the 20th century, the medical community believed that dementia is a mixture of both Alzheimer's disease dementia and vascular disease dementia. In the beginning of the 21st century, on the basis of pathological examination of brain tissues, symptomatology, and the different patterns of brain metabolic activity, a number of other types of dementia have been identified and differentiated from the above two types.

Now, dementia is an umbrella term for several brain diseases that manifest themselves by a group of symptoms affecting memory, other cognitive abilities, and behavior. Pictorially, that umbrella includes the following dementia types: Alzheimer's disease (accounting for ~ 50%-75% of cases or one in every nine people aged 65 and over), vascular disease (~ 20%-30%), Lewy body (~ 10%-25%), frontotemporal (~ 10%-15%), and others. According to *Global Health Estimates*, in 2016, dementia was the fifth global cause of death, climbing up in rank since then.

On The Causal Etiology of Dementia

What is the situation today? The causal etiology of many types of dementia, including Alzheimer's, still remains unclear. Whereas much is known about the disease and its underlying and contributing factors, and much has been published on the subject, we still do not understand the deep biology of the disease. Lacking this understanding, we have so far failed to find a cure and continue to be limited to symptomatic treatments that have limited or no effect. To be sure, many hypotheses have been advanced but these are largely based on risk factors, correlations or associations. But, risk factors, correlations, associations, and the like ... are not causation! Likewise, risk management and symptomatic treatments... are not cure, only palliation! What is going on? Have we got the cause of dementia all wrong? I believe so for, rather than remaining focused on the primary endpoint of a cure, we have meandered around and shifted the emphasis to surrogate endpoints, even though the latter had not been clinically demonstrated to correlate well with the disease. In brief, we lost the proverbial forest for the trees! Yet, hundreds of clinical trials have been undertaken and billions of dollars are being spent each year in rising healthcare costs relating to dementia, in addition to the financial and emotional burdens on families, friends, and care partners/givers. Irrespective of geographical location, racial/ethnic background, and cross-cultural and socioeconomic divides, one can die prematurely of dementia because there still are no cures or effective long-term treatments.

The different types of dementia can be categorized according to (1) the affected brain area(s), (2) their progressiveness and irreversibility, (3) their derivability from another disorder (primary or secondary), and (4) their reversibility. For example, for Alzheimer's disease dementia, the affected brain areas include the outer cortex, the corticobasal area, the hippocampus, and the olfactory cortex. It is progressive/irreversible, not derivable from any other primary disease. No less than 24 disorders are contributing to dementia, some of which being confounding factors that have precluded so far the identification of the root cause of dementia and hindered its diagnosis. While each form of dementia has its own risk factors, most forms have several risk factors in common. These are: age (the strongest known risk factor) although dementia is not a normal part of aging, family history, lifestyle, and pre-existing conditions (such as high blood pressure, diabetes). It is not known how treatment for these problems influences the risk of developing dementia. In addition, more than one type of dementia may exist in the same person. Dementia evolves in three consecutive phases (early, middle, and late phase) ending up in near total dependence and inactivity, serious memory disturbances, and more obvious physical signs and symptoms.

Signs and symptoms are slow and progressive and vary across types and stages and also with the individual. Common symptoms are: impairment of memory, other cognitive abilities, behavioral and emotional problems, language difficulties, and decreased motivation. However, memory loss by itself does not mean having dementia; rather, it is an indication of the need for professional treatment. Also, behavioral and psychological symptoms occur almost always in all types of dementia and may manifest as: agitation/aggression, anxiety, apathy, appetite changes, behavioral changes, delusions/hallucinations, depression, disinhibition, impulsivity, irritability, mood elations, motor abnormalities, psychosis, and sleep disturbances. Lastly, long-term and often gradual decrease in the ability to think and remember may be great enough to interfere significantly with a person's ability to maintain activities of daily living. However, it seems as though people who remain physically active, socially connected, and mentally engaged may be less likely to fall prey to dementia (or develop it later than others). Because symptoms are very similar in all types of dementia, they cannot by themselves help in reaching the correct diagnosis. Beyond the main contributors (Alzheimer's, vascular, Lewy body), the diagnosis may become more elusive when some of the many contributors to dementia enter.

On Reversible Forms of Dementia

Thankfully, it appears that some conditions contributing to dementia may be potentially reversible. These include: Hypothyroidism, vitamin B12 deficiency, Lyme disease, neurosyphilis, and importantly toxicants' exposure and bioaccumulation. The escalating health threats posed by exposure to toxicants has not been sufficiently recognized because it was believed that they are readily eliminated by the body. Yet, the continuous exposure to them, their increasing concentrations, and their long half-lives cause their bioaccumulation in various organs, resulting in various pathologies. Genius and Kelln have identified the following harm mechanisms: "mitochondrial damage, oxidative stress, cell death, neurotransmitter dysregulation, endocrine disruption, and epigenetic modification". These authors

have also pointed out potential treatments based on the elimination of these toxicants. They have further discussed a case report study of a single patient who presented with a significant burden of lead owing to his past occupational exposure. Tests performed to assess the levels of toxicants revealed elevated values of ferritin, immunoglobulin E, C-reactive protein, and creatinine. They also revealed positive antinuclear antibody and decreased glomerular filtration rate. Through interventions to excrete the excessive lead (skin depuration, oral DMSA, and EDTA) and nutritional supplementation (to prevent mineral deficiency), the patient reportedly recovered his good health within one year and progressively resumed a normal life with good quality after six years of therapy.

We should dedicate determined efforts to eliminating those potentially reversible dementia forms that are due to continual exposure to toxicants and their bioaccumulation. Detoxification therapies exist, have been proven in a variety of cases, and need to be made more widely known and available. However, while actively eliminating such potentially reversible conditions will help mitigate some of the effects of the coming dementia pandemic, the major stumbling block remains eradicating the root cause of dementia. Unfortunately, to this date, such has not been the case, notwithstanding the enormous intellectual and financial efforts expanded. In that regard, and since 2017, I have posited that neurodegenerative diseases, including dementia in many of its forms, are but the consequence of an autoimmune disease in overdrive. For example, the generally accepted amyloid-beta protein deposits (or plaques), including interactions between them and neurofibrillary tangles, may only be the signs of a brain homeostasis that had broken down under an avalanche of brain insults (cytokine or/and chemokine storms). I have also charted a path to a cure.

A Prescription for a Cure

The above situation is reminiscent of that for other diseases, particularly cancer. Thus, it may be of interest to first recall our past experience with immunotherapy as a cancer treatment. It was not until after we came to the realization that cancerous cells like healthy cells from which they evolve are braided in our genome, and that cancer is not an organ disease but the result of multiple genetic mutations, i.e., understanding the deep biology of cancer, that we have made great strides in cancer treatment and cure. Witness the emergence of immuno-oncology and the recent (U.S.) FDA-approved use of chimeric antigen receptor (CAR) T-cells to treat certain forms of melanoma. Immunotherapy has been successful in inducing long-term remissions of hard-to-treat cancers. The early identified protein receptor on the surface of T-cells (the cytotoxic T-lymphocyte antigen 4, CTLA-4) and a molecule (named programmed death 1, PD-1) led to astonishing tumor shrinkage and increased survival, particularly in metastatic melanoma. Thus, anti-CTL-4 cells and anti-PD-1 molecules have opened up new vistas in tumor treatment. Beyond that, genetically-modified patient's T-cells and PD-1 molecules promise to be even more effective in specifically tailoring the treatment to the patient along the precepts of personalized medicine.

Natural Immunotherapy with Natural T_{reg} Cells

In parallel with immunotherapy as an emergent therapy of cancer, I advanced earlier the opinion that brain immunotherapy should also become a similar therapy for brain cancers and neurological disorders, providing a paradigm shift in our therapeutic approach to brain cancer and these disorders. The approach advocated here would be to regulate the underlying autoimmune system, to boost in a measured manner the synaptoclastic signals while at the same time taming down the synaptoblastic signals. This idea builds upon work done in diabetes type I, an incurable disease so far, in which the autoimmune system is taught to tolerate the insulin-producing cells of the pancreas so that it does not destroy the diabetic patient's ability to produce the glucose-regulating insulin. The similar idea forms the basis of various clinical trials for treating other incurable diseases such as multiple sclerosis and Graves' disease. The overarching purpose is to harness the hyperactive autoimmune system. This can be accomplished in two manners by employing naturally existing molecules, which can induce an immune response (antigens), or employing engineered immune cells to train the autoimmune system to tolerate the process or tissue it is on track to damage.

The above idea has the potential to cure a range of autoimmune disorders, including especially neurological and neurodegenerative disorders, and particularly dementia. This requires a deep understanding of the molecular basis of autoimmunity, including brain and central nervous system immunity, as well as advances in genetic engineering and cell-based therapy. Caution must

nonetheless be exercised as deploying the immune system to treat certain diseases can also potentially trigger other autoimmune diseases, e.g., in the case of cancer, it may additionally trigger rheumatoid arthritis and colitis. The main immune players are the regulatory T-cells (T_{reg}), which act as the brakes of the immune system. Similarly to other T-cells, T_{reg}-cells rein in the immune cells that are doing damage. It has been suggested that the body can be made to produce the T_{reg}-cells required to dampen a certain autoimmune response by dosing people who are affected with the same antigen or antigens that the immune system wrongly interprets as a reason to attack. This was tested for multiple sclerosis, demonstrating less brain inflammation. The approach is similar to vaccination without the immune-system stimulants called adjuvants that are usually included in vaccine formulations. Here, antigens can induce a calming effect through T_{reg}-cells.

Synthetic Immunotherapy with Engineered T_{reg} Cells

There may be other ways to temper a rogue autoimmune system. For example, in cell-based therapy, a patient's T_{reg}-cells can be removed from the body, engineered to respond to specific antigens that have been wrongly recognized by the immune system as being foreign, and then returned to the body. This is the very principle of the FDA-approved (CAR) T-cells (here T_{reg}-cells) that have been applied to cancer treatment.

Stem Cell Therapy

Stem cell therapy is the use of stem cells to treat or prevent a disease or condition. One of the oldest form of it is bone marrow transplantation that has been used for many years without controversy. We must appreciate the advantages and disadvantages of this other form of therapy and its potential application for the treatment of neurodegenerative diseases including dementia. Of particular interest are regenerative treatments and the treatment of neurodegenerative conditions. In regenerative treatment, stem cells mediate repair via five primary mechanisms (providing an anti-inflammatory effect; homing-in onto damaged tissues and recruiting other cells - usually, endothelial progenitor cells that are necessary for tissue growth; supporting tissue remodeling over scar formation; inhibiting apoptosis; and differentiating into bone, cartilage, tendon, and ligament tissue). To further enrich blood supply to the damaged areas, and consequently promote tissue regeneration, platelet-rich plasma could additionally be used in conjunction with the therapy. The efficacy of some stem cell populations may be affected by the method of delivery. The advantages of stem cell therapy include: lessening the symptoms or conditions and allowing patients to reduce their drug intake.

In the case of neurodegenerative diseases, it is known that healthy adult brains contain neural stem cells, which divide to maintain general stem cell numbers, or become progenitor cells. In healthy laboratory animals, progenitor cells migrate within the brain and function primarily to maintain neuron populations for olfaction. In these animals, research has been conducted on the effects of stem cells on brain degeneration including such brain diseases as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and multiple sclerosis. Of particular note, pharmacological activation of endogenous neural stem cells has been reported to induce neuroprotection and behavioral recovery in adult rat models.

There are, unfortunately, several potential disadvantages: In the case of cancer, the treatment may require immunosuppression before transplantation,; this is in order to perform a preliminary radiation treatment to kill previous cancerous cells or because the patient's immune system may target the stem cells considering them as foreign bodies (but this could be avoided using stem cells from the same patient); pluripotency in certain stem cells could make it difficult to obtain a specific cell type; not all cells in a population differentiate uniformly, making it difficult to obtain the exact cell type needed; undifferentiated cells can create tissues other than the desired types; and pluripotent stem cells can form tumors, which is particularly the case for embryonic, fetal, and induced pluripotent stem cells . In the case of neurodegenerative diseases, including especially dementia, stem cells have been shown to have a low immunogenicity due to the relatively low number of major histocompatibility complex (MHC) molecules found on their surface. They have also been found to secrete chemokines that alter the immune response and promote tolerance of the new tissue. Notwithstanding this low immunogenicity of stem cells, I would still advocate stem cell therapy for the treatment of dementia only under the following conditions: A prior radiation treatment is not required so as not to suppress the immune system, minimizing the secretion of chemokines so as not to adversely alter the immune response, and minimizing if not eliminating any possibility of inducing cancer.

In conclusion, as we are entering a dementia pandemic that may devastate world's economies and health care systems, it behooves us to focus on the causal etiology of neurodegenerative diseases including dementia. While under critical review, my runaway autoimmune disease theory may hopefully provide the needed ultimate treatment that may utilize natural or artificial immune cells or/and stem cells.

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