Current Trends in Biomedical Engineering & Biosciences
ISSN: 2572-1151

Juniper Publishers
key to the Researchers

Review Article
Volume 22 Issue 4 - March 2024
DOI: 10.19080/CTBEB.2024.22.556091

Curr Trends Biomedical Eng & Biosci

Dementia- A Review of the Research and Therapeutic Measures

Jack Kushner*

Honorary Professor of Neurosurgery, Annapolis, Maryland , USA

Submission: February 23, 2024; **Published:** March 07, 2024

***Corresponding author**: Jack Kushner, Honorary Professor of Neurosurgery, Annapolis, Maryland , USA

Abstract

As our population ages, we are seeing more and more patients with variations of Cerebral Dementia. This review cites the symptoms, the neuropathology, the various research trials and ideas, the diagnostic exams, and the treatments commonly used.

Keywords:: Cerebral Neurons; Amyloid; Brain Repair; Reprograming; Diagnostic; Neuropathology; Dementia; Axonopathy; Embryonic stem; Postmitotic

Introduction

When discussing a review of the research and therapeutic measures employed while dealing with cerebral dementia, it is necessary to begin with the symptoms and the neuropathology in the brain. One of the first symptoms seen in patients who are beginning to suffer from dementia, is the loss of memory and the inability to carry out routine tasks. Some patients complain about getting lost and being unable to remember how to navigate back to their homes. Some cannot remember where they put their keys nor can they remember the names of their best friends. Many have difficulty just getting dressed in the morning or how to put the keys in their cars which they cannot remember how to drive.

Upon reviewing pathology slides of the brains of patients who died with the clinical symptoms of Alzheimer's disease, one immediately sees senile plaques, neurofibrillary tangles, Lewy bodies, and lots of A4 or beta amyloid deposits in the extracellular and intraneuronal locations. Much of the insoluble fibrous material is phosphorylated tau protein. To make interpretation of the above more complicated is the fact that many patients have amyloid deposits and they do not have any of the symptoms of dementia. Impairment of cerebral function has not been demonstrated to result from amyloid deposits even though a great deal of therapeutic efforts have been aimed at the removal of this accumulation. Furthermore there is no correlation between the amyloid deposits and the location of the neurofibrillary tangles. Many vessels in the brain are surrounded by amyloid which could cause amyloid angiopathy. Most examinations of the brain with Alzheimer's disease show a marked loss of the cerebral cortex and a reduction of the brain weight [1]. Both amyloid plaques and tau neurofibrillary tangles appear in healthy brains decades before clinical manifestations of dementia appear [2]. Lewy bodies can be seen in Cerebral dementia as well as in Parkinson's disease as these dementia syndromes overlap in many clinical features and management. Some consider these as subtypes of an alpha synuclein associated disease spectrum[3]. It has been the dream of some neuroscientists for years to be able to promote regeneration within the human brain, but so far the results have been disappointing. More recently, direct cell reprograming and stem cell products have revived the idea of a better repair and reconstruction of the neural circuits. The history of neural repair will be discussed [4].

The first approach is to restore the functional integrity of cells that are dysfunctional but not lost. This involves using neurotrophic factors and grafted cells. Another method would be to minimize environmental barrier to repair [5,6]. Use of exercise based therapies and cognitive training has been shown to promote endogenous neurogenesis in the brain experimentally. Whether or not this can be translated into clinical benefits is unknown [7]. Repairing the brain with trophic factors will probably not be effective when the disease has advanced to a critical stage. Growth factor cannot work if the patient has lost too many cells as there is nothing to regenerate. (Growth factor is a secreted biologically active molecule that can affect the growth of cells and can promote or inhibit mitosis.) The disease state would interfere with the growth factor.

When the neurons have been lost as a result of degeneration, these cells can be replaced by transplantation into various regions of the brain. This replacement would recreate complex circuits. Clinical trials with transplants of human fetal stratal tissue have been tried, but to date the effects have not been encouraging. But recent trials with human embryonic stem cells and induced pluripotent stem cells seem to have made this approach possible. New technologies show that transplanted cells mature and integrate into the local host circuitry and form functional synapses. Aberrant connectivity could cause epileptic seizures. The brain is more plastic that thought with respect to accepting new neurons and circuitry. Direct neuronal reprograming has made a lot of progress, but it is unknown at the present time how these new approaches will translate in a hospital setting with live patients.

When a neuron loses connectivity with its axon and efferent target, this is called axonopathy. This also removes the neuron from its major source of neurotrophic support and signaling. Then the neurons are more vulnerable to further degeneration. The degenerating neuron becomes even less responsive to support from exogenous factors [8]. In Alzheimer's disease a link has been established between accumulation of a pathogenic protein and the loss of important neurotrophic factor signaling [9].

Studies administering neurotrophic factors and genes to Alzheimer disease patients have demonstrated only weak biological responses. With refined gene therapy there have been no serious safety issues in a decade of clinical research. Can new neurons migrate from a site of injury such as a stroke and replace neurons that have died? New neurons are regenerated in the sub ventricular zone and dentate gyrus after injury or strokes and they can migrate and replace dead neurons. So we know that the adult brain can self-repair after severe injury and the formation of neurons can be stimulated. This might be a novel therapeutic strategy, but so far not for patients with Alzheimer's disease [10].

Another approach in the quest for a treatment for Alzheimer's disease, is to turn non-neuronal cells into neurons with a neurogenic transcription factor (TF) Pax6 [11]. (Transcription factors bind to DNA while growth factors do not. Transcription factors are proteins that help turn specific genes on or off by biding to DNA.) Since then additional neurogenic agents, micro RNA, and small molecules that regulate developmental pathways have been tried. Even mesoderm-derived fibroblasts from mice and humans have been used to convert neurons [12]. This research has now progressed to the point that the reprogramming neurons are becoming feasible targets. Astrocytes which share a common origin with neurons can be converted into functional neurons with one transcription factor while other cells require more than one factor.. Postmitotic cells can be converted into neurons (e.g. liver cells, and postmitotic astrocytes [13].

In order to take advantage of reprograming of somatic cells into neurons it will be necessary to demonstrate that the adult human brain has cell populations that are amenable to direct somatic cell conversion. Fact is that when there are cells in the human cerebral cortex that have pericyte hallmarks, these can be reprogrammed into neuronal cells by retrovirus-mediated coexpression of the transcription factors Sox2 and Mash1. (encoded by the gene ascl1) [14]. Then these induced neuronal cells have the capability of repetitive action potential firing and can be synaptic targets for other neurons. This is another therapeutic possibility for functional conversion of endogenous cells in the human brain [15].

In order to treat Alzheimer's disease, it is important to order some diagnostic exams such as a MRI, Pet scan, and blood tests to determine whether or not there is a vitamin B12 deficiency or a low level of thyroid hormone. A lumbar puncture might be helpful to determine the fluid pressure and whether there are certain proteins in the spinal fluid. One more test might be helpful and that would be an examination for the apolipoprotein E (APOE) e4 allele which is thought to be a common susceptibility gene for Alzheimer disease.. These patients have a higher risk for Alzheimer's disease [16]. If there is a vitamin B12 deficiency or an underactive thyroid, those things can be treated. Medications that can be considered would include acetylcholinesterase inhibitors such as donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon). Meantime (Namenda) can be used for severe Alzheimer's dementia and can be combined with donepezil (Aricept) Newer treatments include using monoclonal antibodies directed against brain amyloid such as aducanumab(Aduhelm) and lecanemab-irmb(Leqembi) [17]. Another treatment under review would be the use of Dasatinib plus Quercetin therapy in adults [18]. Aria is a common side effect that does not generally cause symptoms but can be serious. These symptoms include headache, dizziness, nausea, confusion, and vision changes. Rexulitis has been approved for treatment of agitation associated with dementia.

One thought being studied as a treatment for Alzheimer's disease emanated from Stanford University. They found that when young mouse plasma was infused in aged mice, this 4448 restored memory in older mice. They did infuse plasma into patients and found that the yFFP treatment was safe and was feasible. The results of the study in humans was too small and inconclusive, but they felt that a larger study would be worthwhile [19].

One of the newest and most imaginative treatments comes from West Virginia University Rockefeller Institution under the direction of Dr. Ali Rezai. He has been working on a treatment for Alzheimer's and has devised a helmet for the removal of the amyloid deposits in the brain with ultrasound and the MRI. Since most medication for getting rid of the amyloid cannot penetrate the blood brain barrier, he is advocating the use of a devised helmet with intravenous medication such as Aricept or Exelon. This is exciting and for now the best hope for patients with Alzheimer's disease [20].

Researchers at Tel Aviv University have introduced a new

How to cite this article: Jack K. Dementia- A Review of the Research and Therapeutic Measures. Curr Trends Biomedical Eng & Biosci. 2024; 22(4): 556091. DOI: 10.19080/CTBEB.2024.22.556091

method of identifying Alzheimer's disease symptoms during sleep or anesthesia in patients twenty years before dementia even occurs. They have detected abnormal brain activity in the hippocampus and they have found accumulations of amyloid and tau protein in the hippocampus. Under the guidance of Professor Inna Slutsky who has led this group, the neurosurgeons were able to use Deep Brain Stimulation (DBS) to target a small nucleus in the thalamus which stopped any epileptic activity and prevented memory loss afterward. This technique involves implanting electrodes in the brain and connecting them to a device similar to a pacemaker and generating electrical impulses. They plan clinical trials in humans and hopefully this will represent huge progress in the treatment of dementia [21].

References

1. Braak H, Braak E(1996) Evolution of the neuropathology of Alzheimer's disease, Acta Neurol Scand Suppl 165: 3-12.
2. Braskie MN, Klunder AD(2010) Neurobiol Aging.
3. Jelling K, Korczyn A (2018) Arę dementia with Lewy bodies and Parkinson's disease dementia the same disease? 16(1): 34.
4. Barker RA, Gotz M, Parma M, New approaches for brain repair-from rescue to reprogramming." Department of Clinical Neuroscience and Cambridge Stem Cell Institute, University of Cambridge CB2 OPY.
5. Adam G, Gallo V (2018) The diversity and disparity of the glial scar. Nat Neurosci 21(1): 9-15.
6. Fawcett JW (2015) The extracellular matrix in plasticity and regeneration after CNS injury and neurodegenerative disease. Prog Brain Res 218, 213-226.
7. Chieffi S, Messina G, Villano I, Messina A, Valenzano A, et al. (2017) Neuroprotective Effects of Physical Activity: Evidence from Human and Animal Studies. Front Neurol 8: 188.
8. Bartus RT, Johnson EM(2017) Neurobiology of Disease 97: 169-178.
9. Bruno MA, (2009) Amyloid beta-induced nerve growth factor dysmetabolism in Alzheimer's disease J Neuropath Exp Neuro 68(8): 857-869.
10. Arvidsson A, Collin T, Kirik D, Kokaia Z (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. Nature Medicine 8(9): 963-970.
11. Heins N, Malatesta P, Cecconi F, Nakafuku M, Götz M, et al. (2002) Glial cells generate neurons: the role of the transcription factor Pax6., Nat Neurosci 5(4): 308-315.
12. Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Wernig M et al. (2010) Direct Conversion of fibroblasts to functional neurons by defined factors. Nature 463: 1035-1041.
13. Marro S, Pang ZP, Yang N, Qu K, Wernig M, et al. (2011) Direct lineage conversion of terminally differentiated hepatocytes to functional neurons. Cell Stem Cell 9(4): 374-382.
14. Armulik A, Genove G, Betsholtz C (2011) Betsholtz: Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. Dev. Cell 21(2): 193-215.
15. Karow M, Sanchez R, Schichor C, Masserdotti G, Ortega F, et al.(2012) Reprogramming Pericyte-Derived Cells of the Adult Human Brain into Induced Neuronal Cells, Science Direct 11(4): 471-476.
16. Drzezga A, Grimmer T, Henriksen G, Mühlau M, Perneczky R, et al. (2009) Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. Neurology 72(17): 1487-1494.
17. LeWine HE (2022) Harvard Health Publishing.
18. Ramanan V. Alsenlite :Senolytics for Alzheimer"s Disease. Mayo Clinic Research.
19. Has SJ, Deutsch FK, Tian L, Richardson K, Coburn M, et al. (2019) Safety, Tolerability, and Feasibility of Young Plasma Infusion in the Plasma for Alzheimer's Symptom Amelioration Study. A Randomized Clinical Trial. JAMA Neurology 76(1): 35-40.
20. https://wvumedicine.org/news-feed/news-article/WVU-Medicine/Front-Page/breakthrough-in-treating-alzheimer-s-using-targeted-drug-delivery-reported-in-new-england-journal-of-medicine/ https://wvutoday.wvu.edu/stories/2020/08/06/wvu-rockefeller-neuroscience-institute-expands-pioneering-alzheimer-s-treatment-to-wider-region-of-the-brainhttps://wvutoday.wvu.edu/stories/2020/04/14/wvu-rockefeller-neuroscience-institute-first-in-the-world-to-open-hippocampal-blood-brain-barrier-in-alzheimer-s-patientshttps://apnews.com/article/alzheimer-drug-blood-brain-barrier-5374da9b3ffa7d0047d2dfb2313a547e https://www.wvnews.com/news/wvnews/from-transplants-to-alzheimers-care-wvu-medicine-aims-to-keep-folks-at-home-for-care/article_b03aec43-a047-5c85-b86b-8b474407ecd4.html https://www.youtube.com/watch?v=7hXtxEvLZ_8https://www.youtube.com/watch?v=7BGtVJ3lBdEhttps://www.youtube.com/watch?v=QpYbEIpcnV8
21. Shoob S, Buchbinder N, Shinikamin O, et al. (2023) Nat. Commun 14, 7002.

How to cite this article: Jack K. Dementia- A Review of the Research and Therapeutic Measures. Curr Trends Biomedical Eng & Biosci. 2024; 22(4): 556091. DOI: 10.19080/CTBEB.2024.22.556091

DOI: 10.19080/CTBEB.2024.22.556091

How to cite this article: Jack K. Dementia- A Review of the Research and Therapeutic Measures. Curr Trends Biomedical Eng & Biosci. 2024; 22(4): 556091. DOI: 10.19080/CTBEB.2024.22.556091