BRAIN AND EXERCISE, FUTURE TREATMENT OF ALZHEIMER’S DEMENTIA

BY ANJALI BAIJU

Pass

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ABSTRACT

Dementia is increasingly recognized as one of the most important medical problems in older people. Alzheimer’s disease accounts for almost 60% of all dementias. Dementia is a complex clinical problem with progressive memory loss and orientation associated with other cognitive deficits and neuropsychiatric symptoms. I have researched current and future treatment of dementia, which has thrown some light on the role of brain derived neurotrophic factor or BDNF and its effect on memory. In this research project I would like to propose an exercise-centred approach in prevention and management of dementia. I also would delve into the relationship between dementia and BDNF and propose methods other than exercise that would enhance BDNF levels.

INTRODUCTION

Prevalence of dementia is reported to be rising from 1% at the age of 60 to at least 35% in the age group of 90. Majority of it, at least 60% constituted by Alzheimer’s dementia. It is characterized clinically by progressive memory and orientation loss and other cognitive deficits, including impaired judgment, and decision-making, apraxia and language disturbances. These are typically accompanied by various neuropsychiatric symptoms (i.e. depression, anxiety, apathy, agitation, delusions and hallucinations).

To date, established treatments are only symptomatic in nature; trying to counterbalance the neurotransmitter disturbance of the disease. Symptomatic approaches to AD would include cholinesterase inhibitors and N methyl D aspartate antagonists. The strategy to use cholinesterase inhibitors is to enhance the cholinergic transmission. Cholinesterase is approved for the treatment of mild to moderate dementia.
The once which are in use are Donepezil, rivastigmine and galantamine. N methyl D aspartate antagonist is used in treatment of moderate to severe dementia.

Studies have also shown significant benefit when a combination of cholinesterase inhibitors and N methyl D aspartate antagonists are used in treatment of moderate to severe dementia.

Neuropsychiatric symptoms accompanying the disease are managed by antidepressants and antipsychotics.

Newer treatments under development aim to interfere with pathogenic steps of AD disease in its early stages. Primary histopathological lesions of AD are amyloid plaques; neurofibrillary tangles sand neuronal loss. Mature plaques consist of an amyloid core with surrounding degenerative neurons affected by toxic effect of Abeta. Neurofibrillary tangles consist of hyperphosphorylated tau protein that has assumed a double helical filament configuration.

Various strategies under different stages of trial are Abeta aggregate inhibitors, selective Abeta 42 lowering agents and immunotherapy aiming at amyloid clearance. Drugs interfering with tau deposition and tau phosphorylation are also under trial.

Other strategies under trial are modulation of cholesterol and vascular related risk factors. This is based on the suggestion that a link exists between hypercholesterolemia, cardiovascular disease and AD.

Currently available treatments of dementia are symptomatic and do not decelerate or prevent progression of the disease. However; these therapies demonstrate modest and consistent benefit for cognition, global status and functional ability. To date, many of the advanced disease modifying strategies have been unsuccessful in demonstrating efficacy in final stages of clinical trial.

Another new frontier that the scientists have opened up in tackling AD is by making use of neural stem cells in animal experiments. Neural stem cells are found to improve memory in mice with advanced dementia. Mice with advanced dementia did markedly better after injection of neural stem cells into their brains. Scientists have found that the neural stem cells secreted a protein called brain derived neurotrophic factor (BDNF). This caused existing tissues to sprout new neuritis and improve the connection between the neurons. Ironically it was found that the plaques and tangles did not correlate well with dementia. It may be recalled at this time that diseases modifying pharmacological agents are targeting plaques and neurofibrillary tangles.

These group of scientists have suggested that the crux of the problem is loss of synapses –connections rather than anything else. Neuronal stem cells have helped form new synapses and helped injured neurons back to health. Scientists have also tried direct injection of BDNF, which was helpful not to the level of injecting neural stem cells.

While researching advances in the treatment of dementia I also came across the role of physical exercise in alleviating dementia risk.

Physical exercise, specifically aerobic exercise, is found to attenuate cognitive impairment and reduce dementia risk. In patients with dementia and cognitive impairment, six months of exercise have shown better cognitive scores. After one year of aerobic exercise scientists have documented increase in hippocampus volume, better spatial memory and
attenuation of age related brain grey matter volume loss. Evaluating these patients with functional MRI (magnetic resonance imaging) have shown better connectivity in brain. Animal studies have also shown improving brain plasticity and improving learning outcomes after one year of aerobic exercise. Physical exercise also helped to decrease the cerebrovascular disease risk, which is considered a contributor to dementia. Physical exercise is also found to have an effect on the levels of BDNF, which is widely expressed throughout the human brain. BDNF levels are significantly reduced in brain of AD patients. It is rapidly transported across the blood brain barrier, hence measurement of circulating BDNF would be relevant. Circulating BDNF levels are reduced in AD patients. Also AD patients whose condition is rapidly declining has significantly lower serum BDNF levels than those with gradually declining disease. In healthy young adults, BDNF appears to be released from brain after short term vigorous exercise and after long term endurance training on basis of arterial and venous measurements.

Another proposed marker for AD is insulin like growth factor (IGF1). Aerobic exercise and long term resistance exercise raised IGF1 levels in two trials. Studies have also shown that there is an inverse relation ship between beta amyloid deposit in brain and exercise. It may be recalled that beta amyloid is a primary component of neuritic plaques, which is a neuropathological marker for AD.

Animal studies have also shown prevention of hippocampus tau disease and memory impairment by 6 months of exercise. It is also interesting to note the striking overlap of risk factors of AD and vascular dementia. Exercises attenuate the risk factors for cerebrovascular disease, like diabetes mellitus, hypertension, hyperlipidemia and obesity. Exercise also have beneficial effect on other diseases like osteopenia, bone fractures, depression, anxiety etc.

Scientists have also tried to quantify the exercise that will have a positive impact. Studies have shown 150 minute of moderate aerobic exercise per week was sufficient to be cognitively protective and associated with increased hippocampal volume plus improved spatial memory. Moderate exercise is defined as exercise sufficient to elevate heart rate or peak oxygen uptake to approximately to 60% of maximum.

Choice of exercise is determined by one’s capabilities and interest. If it become too onerous it is more likely to be abandoned.

DISCUSSION

Having gone through various studies by different scientists we have few inferences. As of today, treatment of dementia is symptomatic. BDNF affects memory and cognition. Synapses and connections in brain also affect memory and cognition.

What I propose is an exercise centric BDNF driven approach. I would propose starting this at community level and educating people about the relevance of exercise and its newfound added benefit. People in midlife who are one of our target group is unlikely to throw up any major resistance however people are elderly or who have other illnesses would probably need assistance and may need trainers during early part of the exercise regime. As discussed before what we aim to achieve is moderate aerobic exercise of at least 150 minutes in a week.
Moderate being defined as exercise sufficient to increase heart rate or peak oxygen uptake to be approximately 60% of maximum. One should also be mindful of positive effect on other risk factors of dementia like diabetes mellitus, hypertension, and hyperlipidemia.

Second group of people are those who have family history or who have other predisposing factors that we have already discussed. I propose blood test for them to measure the BDNF level and also MRI to see any changes that can alert us about possible development of dementia. From studies so far done we know both are relevant. Implementations of these tests are going to throw up many challenges. First of all to make some one accept its usefulness which I am sure will need some more firm scientific proof. With the amount of results that we already have it is only matter of time. The other problem is the cost of all these new modalities and the logistics of making them available in community in a large scale. Also the availability of trained personnel who can decide on what is right or wrong. These are issues which needs much more thought. Once the tests are done it is likely to have two outcomes, those with some doubt about disease and other who are normal. I would propose exercise regime for both groups, as it is unlikely to throw up any ethical issues. Those with any doubtful features needs close follow up and possible further tests in six months time to see how they are responding. Those with no features on tests but are undergoing exercise regime only needs testing if they are found to have any new memory or cognitive problems. What happens to people who have some features and are not in any way benefiting from exercise? I propose these groups of people should get the benefit external supply of BDNF. We know BDNF is secreted by neuritic stem cells. Where do we source these stem cells? Research has already found they can be sourced from embryos. This has already opened up a Pandora’s box where large groups of people and various religious group are up in arms as sourcing stem cells are indirectly denying a person a chance to life. Other source of stem cell is amniotic fluid surrounding the fetus. We are unsure as how long they can survive outside the body. Recent researches have demonstrated that it is possible to convert fully differentiated cells back into stem cell state i.e. pluripotency and self-renewal. The main advantages of this are; no ethical issues, stem can be created from same patient, hence no fear of rejection and thirdly it can be in large quantities which is very important when we are looking at life long supply. Currently the researchers are concentrating on efforts that will allow pluripotent stem cells can be differentiated into stem cells of different organs. Other proposal that I have is to give the BDNF is an injection. We know from current research that BDNF crosses blood brain barrier so that it can reach the target. I was unable to reach to any scientific backing for artificial synthesis of BDNF. I would suggest slow graded form of release injection as and when it is available. Once we artificially synthesize and start supplying externally we need to decide as to how much we need to give and in what interval and how long we need to give. This needs further research. One also needs to be cautious about too much of external supply and its likely side effects. One has to be mindful of early warning signs of toxicity. Assuming either the exercise regime or the BDNF supplies have no benefit on a sub group of people, what do we do? I propose they should be given symptomatic treatment that alleviates their symptoms. We already know that cholinesterase inhibitors, which are currently in use, are beneficial. They have been researched enough and are dependable. We know the route of administration, dose and its possible side effects. The role of disease modifying agents, which are in advanced stage of research also needed to be further looked into. The research products have not been tried in humans yet. The target organs in disease modifying agents being experimented are different and hence the possible side effects, dosage and frequency of supply are likely to be quite different.
Last group of people who are already diagnosed to have moderate to severe disease and are on cholinesterase inhibitors also might benefit from exercise regime. Introduction of exercise will need trainers as the patients are already having cognitive impairment. Introduction need be closely monitored and should be in phased manner. I also would propose giving BDNF to these patients either as an injection or by introducing stem cells that would in turn secrete BDNF. Apart from sorting out ethical issues and other difficulties, which I have already discussed, we should bear in mind that we are giving two drugs at a time. What side effects it will have? Will the side effects be compounded? Do they interact each other? These complex issues will need more research. Input from caregivers would be of enormous value in deciding what medications and in what combination patient tolerate the most. Disease progress in this group can be monitored by simple memory test. I do not feel they need to go through rigorous blood tests or scans as the diagnosis is already made. My modest aim in this group of people would be to bring them back to a reasonably independent life. This may sound too optimistic but my limited understanding of the disease makes me think positive.

CONCLUSION

In summary exercise together with its effect on BDNF production will possibly represent the future of dementia treatment and prevention. Both the role of exercise and effect of BDNF have got scientific footing. While exercise is unlikely to come up with any major ethical issues we should bear in mind that sourcing of BDNF from embryonic stem cell has ethical issues associated with it. Induced pleuripotential stem cell might take care of this to
a large extend. I also would like to highlight the role of Alzheimer’s society UK\textsuperscript{12} which is doing enormous work in terms of day care homes, home care, telephone services, research, training and raising awareness. I would suggest exploring the possibility of using day care centers and trained manpower when we introduce the exercise regime for first time in advanced dementia patients. Patient reception of these would also be better when they are in groups. Finding money for research purposes is likely to be lesser problem than finding money for ongoing care. Government and voluntary organizations are pulling their weight finding funds. Alzheimer’s society of UK has collected 71millions during 2012 financial year;\textsuperscript{12} this in financially difficult times is commendable. National institute of health in US has spent 137 million in 2010 for embryonic stem cell research.\textsuperscript{13} These figures do indicate the seriousness with which the community and the governments at large see the enormity of the problem.

While acknowledging that the research process and its implementation are painfully long and immensely costly, what could be more joyful and gratifying than giving back his or her fading memory?

Summing up I am confident that dementia will form the long list of diseases tamed by mankind, and who knows exercise might lead the way.
REFERENCES :


15. http://www.nature.com Image 2