

Available online at www.sciencerepository.org

Science Repository



Research Article

Physical Therapy for Neurodegenerative Diseases: An Educational Approach

Ashok Chakraborty^{1*}, Ayan Chakraborty², Kylie Smith², Debjit Chakraborty³ and Smita Guha⁴

¹Sacred Heart University, Fairfield, Connecticut, USA

²St. Augustine University of Health Science, Austin, Texas, USA

³NICED, ICMR, West Bengal, Kolkata, India

⁴St. John's University, New York, USA

ARTICLE INFO

Article history:

Received: 13 August, 2020

Accepted: 27 August, 2020

Published: 4 September, 2020

Keywords:

Alzheimer's disease

Parkinson's disease

neural cells

dopamine

neurodegeneration

dementia

ABSTRACT

The most progressive neurodegenerative disease so far we know are Alzheimer's disease (AD) and Parkinson's disease (PD). They manifest cognitive and motor disorders, respectively. No cures are found yet for both the diseases, except some palliatives. At this stage, some alternative measures can be adopted that may slowdown the further progression and may bring comfort to the affected people. Epidemiological data supports a direct relationship between the physical activity (PA) and the risk of developing those two diseases. Aerobic physical exercise (PE) induces the release of neurotrophic factors, promotes angiogenesis, neurogenesis and synaptogenesis, and improves memory and cognitive functions. Further, PE activates the superoxide scavengers, like superoxide dismutase, endothelial nitric oxide synthase, and thereby protects the hippocampus, which is involved particularly in memory function. AD and PD not only deteriorate the quality of life but also may cause death. Therefore, any positive impact of non-pharmacological interventions, such as physical activity and exercise, would improve public health.

© 2020 Ashok Chakraborty. Hosting by Science Repository.

Introduction

Alzheimer's disease (AD) is characterized by a progressive and irreversible memory loss and ultimately develops cognitive impairment and dementia, among the elderly people [1]. Parkinson's disease (PD) mainly affects motor functioning neurons located at the substantia nigra (SN), which secrete dopamine [2]. Generally, AD patients suffer from forgetfulness to gradual memory loss and often cannot recognize their loved ones and some even cannot identify their own house or belongings. The PD patients suffer from slow movement, difficult postures, and memory loss too at the end. The worldwide number of PD and AD cases are growing substantially every year due to the lack of cure [3-5].

The molecular pathogenesis of both the diseases involves proteinopathy (abnormal accumulation of misfolded proteins), mitochondrial

dysfunction and oxidative stress. In case of AD, the amyloid beta ($A\beta$) protein is aggregated, while misfolding and aggregation of α -synuclein have been found in PD [6]. People with PD have low dopamine level in the brain which causes the motor neuron defects, and at the long run can develop dementia in them.

Therapies used today are only palliative, and unable to stop or cure the diseases, PD or AD, either. In this scenario, some other types of management of the diseases can be considered, which can improve a patient's quality of life at least. There are various management steps for controlling these disease progressions, like, regular exercise, healthy diet, mental stimulation, good sleep, stress management, etc. However, we will be restricting our discussion in this article only to physical activity, though all those factors are somehow inter-related [7].

*Correspondence to: Ashok Chakraborty, Ph.D., Sacred Heart University, Fairfield, Connecticut, USA; E-mail: chakrabortya@sacredheart.edu, ashok.chakraborty@yale.edu

Discussion

I Important Factors That Should be Considered for AD and PD Therapies and/or Management

- i. **Dopamine:** Low Dopamine Levels develop PD, and also can cause an increased risk of Alzheimer's Disease (Link). Highly sensitive MRI scans revealed a smaller amount of dopamine in the hippocampus that results in a decreased memory performance.
- ii. **BDNF:** Brain-derived neurotrophic factor (BDNF) protein belongs to the neurotrophin growth factor family has been the focus of interest in AD and PD for a number of years. BDNF improves the survival and function of cholinergic neurons of the basal forebrain, as well as Dopaminergic neurons in the hippocampus and cortex [8].
- iii. **GDNF:** Glial Cell-derived neural factor (GDNF), another important protein of the neurotrophin family, helps in the development, survival, and maintenance of midbrain dopaminergic neurons [9, 10]. However, the function of GDNF on age-related cognitive deterioration, if any, has not been known yet [11]. However, it was shown in animal model that reduced levels of GDNF can induce excess glutamate release, deregulation of glutamate transporter-1, and causes excitotoxicity in the nervous system that precedes dopaminergic degeneration [12].

Further, it was shown before that GDNF can prevent both neurons and glial cells from oxidative stress [13-15].

II What and How Physical Exercise (PE) Can Help in Prevention of AD and PD

The regular and repeated consistent and timely exercise increases cerebral blood flow that contributes to angiogenesis, neurogenesis, synaptogenesis, and neurotransmitter release in different cerebral areas involved in cognition (e.g., memorization) and mobility [16, 17]. Experimental data support that PE can protect against the onset of AD and PD [18-21]. Indeed, physical inactivity is one of the most prominent risk factors for dementia, Parkinson's disease and Alzheimer's disease (AD) [22-29].

i Beneficial Effects of Physical Exercise (PE) on Alzheimer's Disease (AD)

A meta-analysis done in 2009 concluded that PE reduced the risk of developing AD substantially [30]. An American study with 1,740 subjects older than 65 years found that dementia was far less in participants who regularly did walking, cycling, swimming, aerobics, strength training, stretching, or other activities than who did none or occasionally. Therefore, it is strongly supportive that PE is a clinically relevant option towards the prevention of AD.

ii What Kind of PE Program is the Best for AD Control

- a. Aerobic PE is practical and feasible for AD subjects, and they are associated with better cognitive function [31-35].

- b. PE, including power training, improves the low muscle mass and strength which are associated with AD patients [36].
- c. Balance training improves the postural defects in AD patients, and thus reduce the risk of falling at a later stage [37].
- d. PE with treadmill and stair-climbing for a period of 12 weeks increases the cerebral blood flow in the dentate gyrus of the hippocampus, which may improve neurogenesis [38].
- e. In an animal experiment using the transgenic AD-mouse model, the benefits of aerobic physical exercise on synapse, redox homeostasis, and general brain function support the value of PE against neurodegeneration [39].

iii Other Aspects Related to Physical Exercise in Relation to AD

- a. Research with AD patients, it was found that walking with a friend and joining in a conversation has a better preventive effect than walking alone, suggesting that the "socialization effect" of exercise is an important aspect for AD population [40].
- b. In an animal model experiment, PE exhibited a greater reduction in the concentration of amyloid plaques (or A β -plaques) in AD brain and corrects the memory impairment [41].

iv Beneficial Effects of Physical Exercise (PE) on Parkinson's Disease (PD)

A large amount of epidemiological data suggest that PE can prevent the development of PD [18, 42]. Two studies found that the risk of developing PD is less in subjects who practiced PE throughout their lives [24, 43]. PE of high intensity such as cycling, performing aerobics, playing tennis and weight lifting has been shown not only to improve the muscle strength but show a 40% lower risk of having PD than those who did not practice PA or who practiced a low-intensity of PA [44]. A meta-analysis by Herman *et al.* suggests that walking on a treadmill can improve the spatiotemporal parameters of walking [45].

Tai Chi practiced by patients with mild-to-moderate PD can improve postural stability and functional capacities more than the activities of strength training and stretching in them [46]. However, the benefits of PE on fall prevention remain to be determined for PD-affected subjects [47, 48].

III Neuroprotective Mechanisms Induced by Physical Exercise on AD, PD Subjects

- i. It has been shown in mouse model that PE can induce dopamine production as well as stimulates the expression of several neurotrophic factors and angiogenesis [16].
- ii. PE can increase the plasma concentration of brain-derived neurotrophic factor (BDNF) in older healthy subjects [49, 50].
- iii. The loss of dopamine-producing neurons is diminished in PD mice after 18 months of continued PE. Those mice also manifested an improved movement-balance coordination [51].
- iv. Mechanistic investigations revealed that PE, as it increases the cerebral level of BDNF and GDNF, can restore the mitochondrial function and ultimately the neuronal and behavioural recovery generated [51].

Conclusion

Regular physical activity in a planned way can increase the endurance of cells and tissues to oxidative stress, energy metabolism, vascularization, and neurotrophin release; all are important in brain plasticity, neurogenesis, and memory improvement. Although the mechanisms are not clear yet, but it is evident that physical exercise is beneficial for the prevention of AD and PD. Physical exercise decreases the toxin-induced DAergic neuronal loss in mouse models and improves the PD symptoms in them. In AD model, PE improves learning, neurogenesis and restores hippocampal volume, reduces aggregation effectively [52]. However, the nature of optimal PE that should be practiced in order to limit the evolution of AD/PD pathologies, future studies will need to assess the impact of the intensity, duration, and frequency of different exercises. The purpose of this paper is to lay an educational approach to the patients and to the people who are associated with the patients regularly. The main idea is to encourage people to start the habit of practicing regular and timely exercise early on to avoid these diseases.

Acknowledgements

We acknowledge all our colleagues for their help during the preparation of the manuscript by providing all the relevant information.

Funding

None.

Author Contributions

All the authors have contributed equally to prepare this article, read and approved the final manuscript.

Conflicts of Interest

None.

Ethical Approval

Not applicable.

REFERENCES

- Gary L Wenk (2003) Neuropathologic changes in Alzheimer's disease. *J Clin Psychiatry* 64: 7-10. [Crossref]
- Ibañez V Les (2005) Maladies neuro-dégénératives: problèmes cliniques. *Med Nucl* 29: 213-219.
- Cleusa P Ferri, Martin Prince, Carol Brayne, Henry Brodaty, Laura Fratiglioni et al. (2005) Global prevalence of dementia: a Delphi consensus study. *Lancet* 366: 2112-2117. [Crossref]
- Lonneke M L de Lau, Monique M B Breteler (2006) Epidemiology of Parkinson's disease. *Lancet Neurol* 5: 525-535. [Crossref]
- E R Dorsey, R Constantinescu, J P Thompson, K M Biglan, R G Holloway et al. (2007) Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 68: 384-386. [Crossref]
- Makoto Hashimoto, Edward Rockenstein, Leslie Crews, Eliezer Masliah (2003) Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer's and Parkinson's diseases. *Neuromolecular Med* 4: 21-36. [Crossref]
- Melinda Smith, Lawrence Robinson, Jeanne Segal (2019) Preventing Alzheimer's Disease. *Help Guide*.
- Mathew Blurton Jones, Masashi Kitazawa, Hilda Martinez Coria, Nicholas A Castello, Franz Josef Müller et al. (2009) Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci U S A* 106: 13594-13599. [Crossref]
- C Deister, C E Schmidt (2006) Optimizing neurotrophic factor combinations for neurite outgrowth. *J Neural Eng* 3: 172-179. [Crossref]
- L F Lin, D H Doherty, J D Lile, S Bektesh, F Collins (1993) GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* 260: 1130-1132. [Crossref]
- M Pertusa, S García Matas, H Mameri, A Adell, T Rodrigo et al. (2008) Expression of GDNF transgene in astrocytes improves cognitive deficits in aged rats. *Neurobiol Aging* 29: 1366-1379. [Crossref]
- Wataru Matsunaga, Kenichi Isobe, Tetsuya Shirokawa (2006) Involvement of neurotrophic factors in aging of noradrenergic innervations in hippocampus and frontal cortex. *Neurosci Res* 54: 313-318. [Crossref]
- C C Chao, E H Lee (1999) Neuroprotective mechanism of glial cell line-derived neurotrophic factor on dopamine neurons: role of antioxidation. *Neuropharmacology* 38: 913-916. [Crossref]
- Henrich Cheng, Yu Show Fu, Jiun Wen Guo (2004) Ability of GDNF to diminish free radical production leads to protection against kainate-induced excitotoxicity in hippocampus. *Hippocampus* 14: 77-86. [Crossref]
- C M Fox, D M Gash, M K Smoot, W A Cass (2001) Neuroprotective effects of GDNF against 6-OHDA in young and aged rats. *Brain Res* 896: 56-63. [Crossref]
- Michael J Zigmond, Judy L Cameron, Barry J Hoffer, Richard J Smeyn (2012) Neurorestoration by physical exercise: moving forward. *Parkinsonism Relat Disord* 18: S147-S150. [Crossref]
- Zsolt Radak, Nikoletta Hart, Linda Sarga, Erika Koltai, Mustafa Atalay et al. (2010) Exercise plays a preventive role against Alzheimer's disease. *J Alzheimers Dis* 20: 777-783. [Crossref]
- Fernando Alonso Frech, Juan Juni Sanahuja, Amelia Mendoza Rodriguez (2011) Exercise and physical therapy in early management of Parkinson disease. *Neurologist* 17: S47-S53. [Crossref]
- A S Buchman, P A Boyle, L Yu, R C Shah, R S Wilson et al. (2012) Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* 78: 1323-1329. [Crossref]
- Steven Karceski (2012) Preventing Alzheimer disease with exercise? *Neurology* 78: e110-e112. [Crossref]
- Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 13: 788-794. [Crossref]
- Kirk I Erickson, Ruchika S Prakash, Michelle W Voss, Laura Chaddock, Liang Hu et al. (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus* 19: 1030-1039. [Crossref]
- Laura E Middleton, Arnold Mitnitski, Nader Fallah, Susan A Kirkland, Kenneth Rockwood (2008) Changes in cognition and mortality in

- relation to exercise in late life: a population based study. *PLoS One* 3: e3124. [Crossref]
24. H Chen, S M Zhang, M A Schwarzschild, M A Hernán, A Ascherio (2005) Physical activity and the risk of Parkinson disease. *Neurology* 64: 664-669. [Crossref]
25. A J Sasco, R S Paffenbarger Jr, I Gendre, A L Wing (1992) The role of physical exercise in the occurrence of Parkinson's disease. *Arch Neurol* 49: 360-365. [Crossref]
26. Carl W Cotman, Nicole C Berchtold (2007) Physical activity and the maintenance of cognition: Learning from animal models. *Alzheimer's Dement* 3: S30-S37. [Crossref]
27. M Kivipelto, A Solomon (2008) Alzheimer's disease – the ways of prevention. *J Nutr Health Aging* 12: 89S-94S. [Crossref]
28. Eric B Larson (2008) Physical activity for older adults at risk for Alzheimer disease. *JAMA* 300: 1077-1079. [Crossref]
29. Christianna Purnell, Sujuan Gao, Christopher M Callahan, Hugh C Hendrie (2013) Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. *Alzheimer Dis Assoc Disord* 23: 1-10. [Crossref]
30. M Hamer, Y Chida (2009) Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med* 39: 3-11. [Crossref]
31. Fang Yu, Ruth M Swartwood (2012) Feasibility and perception of the impact from aerobic exercise in older adults with Alzheimer's disease. *Am J Alzheimers Dis Other Dement* 27: 397-405. [Crossref]
32. Kristine Yaffe (2010) Biomarkers of Alzheimer's disease and exercise: one step closer to prevention. *Ann Neurol* 68: 275-276. [Crossref]
33. Yonas E Geda, Rosebud O Roberts, David S Knopman, Teresa J H Christianson, V Shane Pankratz et al. (2010) Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch Neurol* 67: 80-86. [Crossref]
34. T Archer (2011) Physical exercise alleviates debilities of normal aging and Alzheimer's disease. *Acta Neurol Scand* 123: 221-238. [Crossref]
35. Eric D Vidoni, Angela Van Sciver, David K Johnson, Jinghua He, Robyn Honea et al. (2012) A community-based approach to trials of aerobic exercise in aging and Alzheimer's disease. *Contemp Clin Trials* 33: 1105-1116. [Crossref]
36. Ben F Hurley, Erik D Hanson, Andrew K Sheaff (2011) Strength training as a countermeasure to aging muscle and chronic disease. *Sports Med* 41: 289-306. [Crossref]
37. Keith D Hill, Dina LoGiudice, Nicola T Lautenschlager, Catherine M Said, Karen J Dodd et al. (2009) Effectiveness of balance training exercise in people with mild to moderate severity Alzheimer's disease: protocol for a randomised trial. *BMC Geriatr* 9: 29. [Crossref]
38. Ana C Pereira, Dan E Huddleston, Adam M Brickman, Alexander A Sosunov, Rene Hen et al. (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A* 104: 5638-5643. [Crossref]
39. Yoelvis García Mesa, Juan Carlos López Ramos, Lydia Giménez Llort, Susana Revilla, Rafael Guerra et al. (2011) Physical exercise protects against Alzheimer's disease in 3xTg-AD mice. *J Alzheimer's Dis* 24: 421-54. [Crossref]
40. R M Tappen, K E Roach, E B Applegate, P Stowell (2000) Effect of a combined walking and conversation intervention on functional mobility of nursing home residents with Alzheimer disease. *Alzheimer Dis Assoc Disord* 14: 196-201. [Crossref]
41. Carla M Yuede, Scott D Zimmerman, Hongxin Dong, Matthew J Kling, Adam W Bero et al. (2009) Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Dis* 35: 426-432. [Crossref]
42. Den'etsu Sutoo, Kayo Akiyama (2003) Regulation of brain function by exercise. *Neurobiol Dis* 13: 1-14. [Crossref]
43. Q Xu 1, Y Park, X Huang, A Hollenbeck, A Blair et al. (2010) Physical activities and future risk of Parkinson disease. *Neurology* 75: 341-348. [Crossref]
44. Evan L Thacker, Honglei Chen, Alpa V Patel, Marjorie L McCullough, Eugenia E Calle et al. (2008) Recreational physical activity and risk of Parkinson's disease. *Mov Disord* 23: 69-74. [Crossref]
45. T Herman, N Giladi, J M Hausdorff (2009) Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. *J Neural Transm (Vienna)* 116: 307-318. [Crossref]
46. Fuzhong Li, Peter Harmer, Kathleen Fitzgerald, Elizabeth Eckstrom, Ronald Stock et al. (2012) Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med* 366: 511-519. [Crossref]
47. Natalie E Allen, Catherine Sherrington, Serene S Paul, Colleen G Canning (2011) Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. *Mov Disord* 26: 1605-1615. [Crossref]
48. Victoria A Goodwin, Suzanne H Richards, William Henley, Paul Ewings, Adrian H Taylor et al. (2011) An exercise intervention to prevent falls in people with Parkinson's disease: a pragmatic randomised controlled trial. *J Neurol Neurosurg Psychiatry* 82: 1232-1238. [Crossref]
49. Kirk I Erickson, Michelle W Voss, Ruchika Shaurya Prakash, Chandramallika Basak, Amanda Szabo et al. (2011) Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A* 108: 3017-3022. [Crossref]
50. Flávia Gomes de Melo Coelho, Thays Martins Vital, Angelica Miki Stein, Franciel José Arantes, André Veloso Rueda et al. (2014) Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *J Alzheimers Dis* 39: 401-408. [Crossref]
51. Yuen Sum Lau, Gaurav Patki, Kaberi Das Panja, Wei Dong Le, S Omar Ahmad (2011) Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. *Eur J Neurosci* 33: 1264-1274. [Crossref]
52. Daniel A Nation, Suzi Hong, Amy J Jak, Lisa Delano Wood, Paul J Mills et al. (2011) Stress, exercise, and Alzheimer's disease: a neurovascular pathway. *Med Hypotheses* 76: 847-854. [Crossref]