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Can immunization with Bacillus Calmette-Guérin (BCG) protect against Alzheimer's disease?

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder which is the most prevalent cause of dementia in the western world. Currently, it is the most expensive disease in America, costing more than heart diseases and cancer and as the world population is getting older it is expected to become the most expensive medical disorder in the world. AD is characterized by three core pathologies: accumulation of amyloid β (Aβ) plaques, neurofibrillary tangles (NFT) and sustained inflammation. It is now believed that inflammation provides the link between Aβ and NFT. The immune system is therefore, a major player in the pathogenesis of AD. Here we propose that Bacillus Calmette-Guérin (BCG) could affect the incidence of AD.

Bacillus Calmette-Guérin (BCG) is a live attenuated *Mycobacterium bovis* preparation first developed as a vaccine against *M. tuberculosis*. It has been shown to be moderately effective in preventing tuberculosis, while noted to induce modifications in inflammatory response and to regulate the immune system. Intra-vesical administration of BCG is used successfully in the past four decades to prevent recurrence of non-muscle invasive bladder cancer.

In this manuscript we investigate the hypothesis that exposure to BCG decreases the prevalence of AD in elderly population and that this occurs through modulation of the immune system. Our hypothesis is based on several lines of evidence: lower prevalence of AD in countries with high BCG coverage, ability of BCG to ameliorate several conditions involving the immune system like type 1 diabetes mellitus and multiple sclerosis, animal models of AD in which BCG shows therapeutic potential and a plausible molecular mechanism which may be the basis for this hypothesis. Namely, elevated systemic levels of IL-2 (as found when BCG is given intra-vesically) that amplify Treg cells that inhibit AD associated inflammation, decreased plaque formation and restore cognitive function. To test this hypothesis one may study cognition in the large available "natural adult population" exposed to high dose of BCG through the bladder. Bladder cancer survivors not given BCG can serve as control group. This population can be used without adding any medical intervention.

Alzheimer's disease

Alzheimer's disease (AD) is the major cause of chronic progressive dementia in the western world accounting for 60–70% of all cases of dementia. It currently affects over 5 million Americans [1] and as the number of people older than 65 is expected to triple between 2000 and 2030 the prevalence of AD is expected to rise accordingly. As a result, the cost of AD care to Medicare and Medicaid is expected to rise from 186 billion dollar in 2018 to 750 billion in 2050 [2].

AD is marked by several characteristic brain pathological features including the accumulation of amyloid β (Aβ) plaques and neurofibrillary tangles (NFT) and sustained inflammation [3]. It is now believed that inflammation is not just a response of the immune system to neuronal loss but a major player in AD pathogenesis. The current accepted role of the immune system in AD is as follows: the presence of Aβ activates microglia cells. They migrate and phagocytiz the Aβ. Early in AD development this process clears the Aβ but later, the microglia are no longer able to process the Aβ. This leads to a condition of sustained activation termed "reactive microgliosis". The results of this process are the sustained production of pro-inflammatory cytokines and neurotoxins. While the ability of the microglia to process the Aβ decreases, their immune activation abilities persist. Thus a continuous loop of neurotoxicity and response to neurotoxicity perdures. In later stages of AD peripheral macrophages are also recruited to the brain further amplifying the pathology. Multiple immune cells and cytokines participate in AD. Worth mentioning are the $CD4^+$ $CD25^+Foxp3^+$ regulatory T cells (Treg). They represent a small proportion of the total lymphocyte population that can regulate immune response critical for maintenance of self-tolerance [4]. These cells have a neuroprotective effect shown in animal models of AD [5]. The key cytokines participating in AD include the pro-inflammatory TNF-α, IL-1β and the double action cytokine IL-6 that in low levels reduces microglia activity and in

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high levels is pro-inflammatory [3,6]. A prominent anti-inflammatory cytokine is IL-10. It is released by microglia and astrocytes and inhibits the production of pro-inflammatory cytokines. Unfortunately, clinical trials with IL-10 therapy failed to show any benefit and in some studies it even exacerbated the disease. Another major player is IL-2. In low doses it selectively expands population of Treg and thus serves as a neuroprotective cytokine [4].

Bladder cancer and the bacillus Calmette-Guérin (BCG)

Bladder cancer is the 6th most common cancer in the western world. Most of these tumors are non-muscle invasive and do not spread beyond the bladder or metastasize. However, they do tend to recur after initial resection at high rates of about 50%. The use of intravesical BCG for preventing recurrence of non-muscle invasive bladder cancer began in the seventies. Since then multiple studies confirmed its efficacy [7]. Despite years of intense research the exact mechanism of its anti-cancer activity is unknown. It is well appreciated however, that BCG bind fibronectin in the bladder wall and stimulates Th1 cell to secrete multiple cytokines including: IL1, 2, 5, 6, 8, 10, 12 and 18, as well as IFNγ, TNFα and GM-CSF. It is presumed that these cytokines induce cell-mediated cytotoxic mechanisms that eliminate cancer cells. The immune response to intravesical instillation of BCG is not limited to the bladder. An increase in the serum levels of IL-2 and IFNγ as well as in BCG-induced killer activity of peripheral blood mononuclear cells has been reported [8].

The hypothesis

Exposure to BCG decreases the prevalence of AD in elderly populations. This occurs through modulation of the immune system. Our hypothesis is based on several lines of evidence.

Rationale supporting the hypothesis

Epidemiological data linking AD and BCG coverage

Table 1 shows age-adjusted Alzheimer + dementia deaths/100,000, BCG coverage and gross domestic product per capita in selected countries. The complete list of 166 countries with available information is provided in the supplement material. As can be seen in the table, there is an inverse relation between BCG coverage and the prevalence of AD and dementia. Regression analysis shows low but highly significant correlation between the two parameters ($R^2 = 0.1$, $p = 1.5E-28$). Countries can be clustered to 4 categories according to the prevalence of AD, the rate of BCG coverage and percentage of population older or younger than 65 years (Table 1). Inside the cluster, high correlations (up to R^2 of 0.9) can be found between AD at death and the % of population older than 65 years (Fig. 1). BCG administration was stopped in the U.S. in the early 60's. Might this herald the rise in AD we currently notice? High socio-economic status (measured roughly by the GDP per capita) is considered a protective factor against AD [9]. Yet countries with high GDP per capita also have high prevalence of AD (Table 1). Therefore, differences in socio-economic status cannot explain the differences in AD prevalence.

Table 1
Age-adjusted Alzheimer + dementia death deaths/100,000, BCG coverage and gross domestic product per capita in selected countries.

Country	Alzheimer Disease + Dementia	BCG coverage	% > 65	Gross domestic product per capita ($)
High AD, Low BCG, High > 65 years				
United Kingdom	49	0	46/330 = 14	44,100
United States	44	0	18	59,500
Sweden	36	25	19.8	51,500
Finland	66	0	20.8	44,300
Low AD, Low BCG, High > 65 years				
Slovakia	20.8 (age adjusted)	0	12.8	34,400
Czech Republic	13	0	18	35,500
Luxembourg	21.7	0	14	106,300
Low AD, High BCG, High > 65 years				
Russia	7	96	13.8	27,800
Lithuania	5	97	19.7	32,300
Albania	19	99	11.9	12,500
Chile	16	96	10.8	24,500
Low AD, High BCG, low > 65 years				
Ethiopia	15	88	3	2,200
India	15	87	3 – 6	7,200
Zambia	11	97	2.3	4,000
Brazil	11	99	3.15. 8.55	15,600
Vietnam	20	97	8.4	6,900
Philippines	2	80	7	8,300

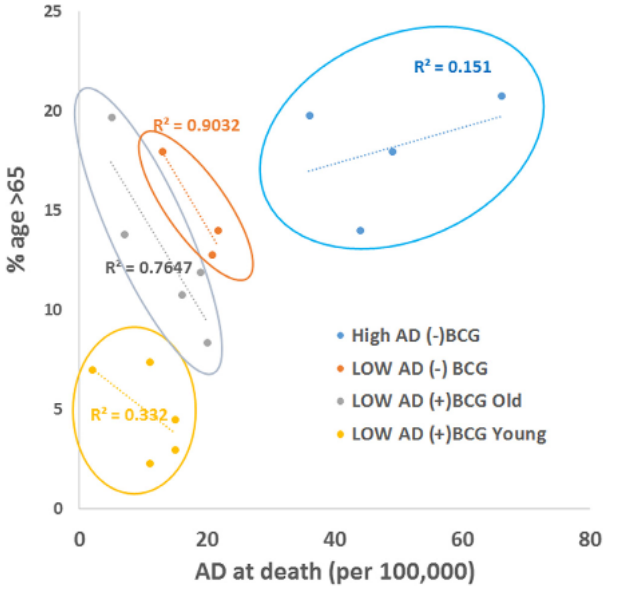

Fig. 1. Percent of population older than 65 years according to AD prevalence at death. Countries are clustered according to their high/low AD prevalence and high/low BCG coverage.

BCG ameliorates AD risk factor-type 1 diabetes mellitus

Diabetes mellitus type 1 is a risk factor for AD [10]. This disease is considered to have a significant autoimmune component. In randomized prospective study, type 1 diabetes patients were given 2 injections of BCG. Prolonged lowered hemoglobin A_{1c} to near normal levels was observed. This happened through a shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis [11].

BCG and multiple sclerosis (MS) and other neuro-inflammatory diseases

BCG immunization affects the course of the inflammatory mediated neurodegenerative disease-multiple sclerosis. Treatment with BCG significantly reduced the number of enhancing lesions in a randomized trial of 82 MS patients given either BCG or placebo [12]. Similar findings were also reported in experimental autoimmune encephalomyelitis [13] and Bercovier H. personal communication).

BCG neutralizes Herpes-a suspected AD microbial trigger

Readhead et al. have found Herpes Simplex DNA embedded in

genomes of AD patients [14] and Itzhaki et al reported an association between AD and the finding of Herpes virus Type 1 in brains [15]. If Herpes is involved in AD, then one may recall the experiments of Hippmann et al. from 1992 showing that BCG is able to reduce the occurrence of herpes lesions, keeping 19% of patients herpes-free for 3 years [16].

The APPPS1 AD mouse model

APPPS1 mice are a transgenic model of AD. These mice develop amyloid plaques deposition at six weeks of age. BCG immunization in this model altered both pathology and cognitive dysfunction [17]. BCG therapy reversed cognitive decline in this model but did not reduces βA burden in the brain. Interestingly, this study also showed enhanced recruitment of inflammation-resolving monocytes across the choroid plexus and perivascular spaces to cerebral sites of plaque pathology, increased circulating IFNγ levels, upregulation of cerebral anti-inflammatory cytokine levels and elevated expression of neurotrophic factors in the brain.

Discussion

In this manuscript we suggest a hypothesis that connects BCG immunization with a lower risk of AD. We based this hypothesis on epidemiological and experimental data. The exact mechanisms of BCG anti-cancer and possible anti-AD effects are yet unknown. We do know however, that intra-vesical BCG increases systemic IL-2 levels [8]. It is also appreciated that IL-2 expands Treg populations [4] and that these cells are neuroprotective [5]. In the APPPS 1 mouse model, active amplification of Treg cells by peripheral IL-2 treatment decreased plaque formation and restored cognitive function [18]. Additionally, changes in the blood-cerebrospinal fluid barrier found in patients with mild cognitive impairment may facilitate the entry of systemic IL-2 into the nervous system [6]. Therefore BCG treatment in elderly people may prevent the development of AD or delay its inception by a few years.

Obviously, association cannot prove causation. None of the evidences presented in the manuscript directly proves an association between BCG immunization and a lower risk of AD. Proving an association however, a may not be extremely difficult as there is a large "natural adult population" exposed to high doses of BCG as part of their bladder cancer therapy. Testing the cognitive status of this population can assist in assessing the hypothesis raised here without adding any medical intervention. Bladder cancer patients not treated with BCG can easily serve as a control group.

Conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Prince M, Comas-Herrera A, Knapp M, Guerchet M, et al. World Alzheimer Report 2016: Improving Healthcare for People Living With Dementia: Coverage, Quality and Costs Now and in the Future. London: Alzheimer's Disease International; 2016.

[2] alzimpact.org.

[3] Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, et al. Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (NY) 2018;4:575–90.

[4] Li Y, Liu X, Wang W, Wang S, et al. Low-dose IL-2 expands $CD4^+$ regulatory T cells with a suppressive function in vitro via the STAT5-dependent pathway in patients with chronic kidney diseases. Ren Fail 2018;40:280–8.

[5] Baek H, Ye M, Kang GH, Lee C, et al. Neuroprotective effects of CD4 + CD25 + Foxp3 + regulatory T cells in a 3xTg-AD Alzheimer's disease model. Oncotarget 2016;7:69347–57.

[6] Ott BR, Jones RN, Daiello LA, de la Monte SM, et al. Blood-cerebrospinal fluid barrier gradients in mild cognitive impairment and Alzheimer's disease: relationship to inflammatory cytokines and chemokines. Front Aging Neurosci 2018;10:245.

[7] Kamat AM, Bellmunt J, Galsky MD, Konety BR, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. J Immunother Cancer 2017;5:80.

[8] Taniguchi K, Koga S, Nishikido M, Yamashita S, et al. Systemic immune response after intravesical instillation of bacille Calmette-Guérin (BCG) for superficial bladder cancer. Clin Exp Immunol 1999;115:131–5.

[9] Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Arch Neurol 1997;54:1399–405.

[10] Whitmer R. Conference coverage, Type 1 Diabetes Increases Dementia Risk. Neurology Reviews. 2015; September; 23:25.

[11] Kühtreiber WM, Tran L, Kim T, Dybala M, et al. Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. NPJ Vaccines 2018;3:23.

[12] Ristori G, Buzzi MG, Sabatini U, Giugni E, et al. Use of Bacille Calmette-Guèrin (BCG) in multiple sclerosis. Neurology 1999;53:1588–9.

[13] Lee JE, Reinke EK, Zozulya AL, Sandor M, et al. Mycobacterium bovis bacille calmette-guerin infection in the CNS suppresses experimental autoimmune encephalomyelitis and Th17 responses in an IFN-γ -independent manner. J Immunol 2008;181:6201–12.

[14] Readhead B, Haure-Mirande JV, Funk CC, Richards MA, et al. Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron 2018;99:64–82.

[15] Itzhaki RF. Corroboration of a major role for herpes simplex virus Type 1 in Alzheimer's disease. Front Aging Neurosci 2018. https://doi.org/10.3389/fnagi.2018.00324.

[16] Hippmann G, Wekkeli M, Rosenkranz AR, Jarisch R, et al. Nonspecific immune stimulation with BCG in Herpes simplex recidivans. Follow-up 5 to 10 years after BCG vaccination. Wien Klin Wochenschr 1992;104:200–4.

[17] Zuo Z, Qi F, Yang J, Wang X, et al. Immunization with Bacillus Calmette-Guérin (BCG) alleviates neuroinflammation and cognitive deficits in APP/PS1 mice via the recruitment of inflammation-resolving monocytes to the brain. Neurobiol Dis 2017;101:27–39.

[18] Dansokho C, Aucouturier P, Dorothé EG. Beneficial effect of interleukin-2-based immunomodulation in Alzheimer-like pathology. Brain 2016;139:1237–51.