Tuberculosis for Alzheimer's: Risk factor, Treatment or Prevention

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ABSTRACT

Alzheimer's disease is a type of dementia and there were 50 million individuals have dementia in 2018 worldwide and the cost of dementia care to Medicare and Medicaid is so high (about US$1 trillion) in that year. Recently, several articles show that tuberculosis may be increased the development rate of Alzheimer's disease in these patients. So knowing the probable relationship between these two could be helpful. Also, there is evidence demonstrating that the Bacillus Calmette–Guérin (BCG) vaccine and rifampicin as a conventional vaccine and medicine against Mycobacterium tuberculosis infections could be used as a promising agent for the prevention and reduce the development of Alzheimer's disease and other neurodegenerative diseases. According to our knowledge, the present review is the first and only review that assessed the possible relationship between tuberculosis and Alzheimer's disease as well as the possible therapeutic role of rifampicin and BCG vaccine in treatment and prevention of Alzheimer's disease, respectively.

Introduction

Alzheimer's is a type of dementia that is a chronic neurodegenerative disease and is a cause of 60–70% of cases of dementia (1,2).

According to the WHO reports, there were 50 million individuals have dementia in 2018 around the world and the cost of dementia care to Medicare and Medicaid is US$1 trillion in that year. There will be one new case of dementia every 3 seconds around the world.

This number is believed to be triple to 152 million by 2050 (3).Tuberculosis (TB) is one of the major cause of death around the world. About 1.7 billion peoplewere latently infected with Myco

bacterium tuberculosis. According to the World Health Organization (WHO), approximately 10 million people are infected with M. tuberculosis and it causes 1.6 million died in 2017 (4,7).

Recently, there is a new controversial approach about microorganisms or bacterial disease such as tuberculosis that could be a responsible and underlying factor in the incidence of Alzheimer's disease. The aim of this article was a comprehensive summary of the possible relationship between tuberculosis and the incidence of Alzheimer's disease.

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literature review
Tuberculosis and Alzheimer's

Some study claim that pulmonary tuberculosis increased the risk of Alzheimer's because TB induces a complex of inflammatory responses in the host and it is now believed that inflammation has a critical role in Alzheimer's disease (8, 9). The infection process of M. tuberculosis resulting in different interaction with the innate immune system then induces a high amount of proinflammatory cytokines such as TNFα, IL-6, IFN-γ and IL-1β)that are critical in a complex interaction between the host immune system and M. tuberculosis (10,12).
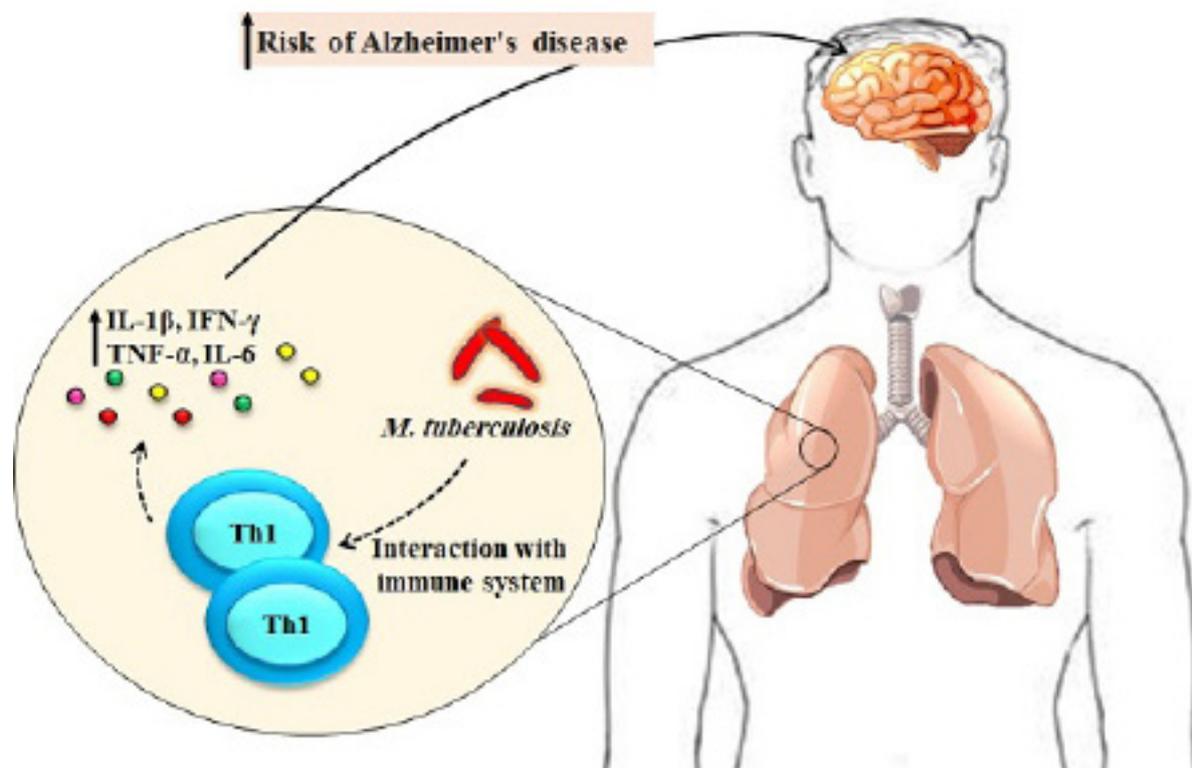
One of the leading cause of dementia is Alzheimer's disease that accounting for about 75% of cases (3). There are some mechanisms that may be responsible or have a role in the development of Alzheimer's including metabolic cascade of amyloid, apolipoprotein E, the hyperphosphorylation of tau protein, oxidative stress, abnormal cell cycle reentry, amyloid β metabolism, and inflammation that associated with infection or injury (13,15).

Although the underlying mechanisms and association of tuberculosis and incidence of Alzheimer's are unclear, but, there is some evidence from previous research that may explain this association.

TNFα and IL-1 β are two proinflammatory cytokines that have a crucial role in the pathogenesis of tuberculosis as well as a subsequent risk of Alzheimer's disease in the elderly.

Furthermore, IL-6 has a double activity that reduces microglia activity at low levels and acted as a pro-inflammatory cytokine in high levels. Microglia cells are active in the presence of amyloid β (Aβ) at the early stage of developing Alzheimer's disease than clear and phagocytize the Aβ also, it released an anti-inflammatory cytokine is IL-10 that hinders the release of pro-inflammatory cytokines (16,18). Later, the microglia are not able to process the Aβ which results in the sustained production of pro-inflammatory cytokines and neurotoxins. Previous reports demonstrate that the overall risk of Alzheimer's disease in the group of a patient living with TB was 1.43 (95%CI= 1.01—2.02) and it higher than a group of a patient without TB (19). Another cohort study in 2015, show that the overall risk of developing dementia among the patients with TB was significantly higher than the non-TB (HR =1.21, 95% CI = 1.05-1.40), also, the follow-up of the patient demonstrates that incidence risk of Alzheimer's in patients with TB has increased by 1.78 (95% CI =1.36-2.32) (20). So according to evidence of the previous study people who live with tuberculosis have a significantly higher risk of developing Alzheimer's in comparison to the general population (Figure 1).

Figure 1: High risk of alzhemers disease in patients with tuberculosis.

Rifampicin and Alzheimer's

Rifampicin, also known as rifampin, used in the treatment of Mycobacterium infections, including tuberculosis, leprosy, and Mycobacterium avium complex. Rifampicin is a lipid-soluble antibiotic that delivers orally then rapidly absorbed and distributed throughout the body tissues and body fluids, including the CSF also, it's able to penetrate into the brain via passing the blood-brain barrier. Furthermore, it's one of the neuroprotective antibiotics and able to stimulate the modulate the neuroinflammatory response in Alzheimer's disease (21).

Several studies demonstrate that rifampicin had effective activity against the accumulation and toxicity of intracellular amyloid-b oligomers (22, 23).

Rifampicin indicated the broad spectrum activity in the area of Alzheimer's therapy due to its ability able to inhibit the oligomer formation of amyloid-b, synuclein and tau protein which detected in the brains of patients with dementia also have a role in the development of Alzheimer's. Animal trial administered that rifampicin could reduce the accumulation of amyloid-b oligomers and tau oligomers which result in improved the memory of the mice (24, 25).

This result indicates that rifampicin could be a promising medicine for the prevention and reduce the advancement of Alzheimer's disease and other neurodegenerative diseases.

BCG and Alzheimer's

Bacillus Calmette-Guerin (BCG) vaccine is the effective immunization against tuberculosis and only TB vaccine in use in many countries. BCG is an attenuated form of Mycobacterium bovis. BCG vaccine provides the well protects against tuberculosis in children but currently not effective against pulmonary TB in adults (26, 27).

In the other hand, BCG vaccine approved by the FDA to use for the preventing recurrence and treatment of non-muscle invasive bladder cancer. It's could bind to the fibronectin in the bladder wall than stimulates Th1 cell to release the several cytokines such as IL1, 2, 5, 6, 8, 10, 12 and 18, IFNγ, TNFα, and GM-CSF (28, 29).

Now there is a hypothesis that BCG could be used as an agent to decrease the incidence and prevalence of Alzheimer's disease in the elderly population by several reasons including there is

low prevalence of Alzheimer's disease in countries with higher coverage of BCG also found the high level of IL-2 in the presence of intravesical BCG that amplify Treg cells. These are able to inhibit the related inflammation with Alzheimer's

disease then reduced the formation of the plaque and restore cognitive function that described as cerebral activities (30,31).

A study in 2019, examined this hypothesis on the animal model and demonstrate that in presence of BCG the level of IL2 increased than active amplification of Treg cells which result in decreased the formation of plaque and restored cognitive function (32).

Therefore, using the BCG as a preventing agent in risk group including the elderly population could be a promising way to decrease or prevent the development of Alzheimer's disease or at least delay its inception by a few years.

Conclusion

To reduce Alzheimer's disease as one of the most common types of dementia in the elderly population, in order better management there is a need to know and find the underlying risk factor such as tuberculosis that develop the risk of Alzheimer's. Also find the new agent to treat, prevent or reduce the development presses of this disease is so important also it could be helpful to reduce the cost of care.

Rifampicin as an available and in use medicine could be promising to prevent or reduce the advancement of Alzheimer's disease. Additionally, BCG could be hopeful in preventing and decreasing the development process of Alzheimer's disease. Furthermore, further studies are necessary to confirm this finding and explore their mechanisms.

Conflicts of interest

The authors declare no conflicts of interest.

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