



Short Communication

Influenza vaccination and dementia risk; an unanticipated benefit?

Eman Ali ^{*}, Asim Shaikh

Dow University of Health Sciences, Karachi, Pakistan

ARTICLE INFO

Keywords:

Influenza vaccine/therapeutic use
Dementia
Alzheimer's disease
Cohort-studies

ABSTRACT

Alzheimer's disease (AD) characterized by cognitive decline and dementia has evolved into source of extreme concern globally, often associated with functional dependence and financial instability before progressing to complete degeneration of neural and motor skills. Despite multiple interventions being available, only few have been able to show clinical efficacy, others not meeting satisfactory efficacy endpoints as more options are being explored. According to various studies, influenza vaccines have shown clinical evidence in being effective against reduction in dementia risk. Multiple large-scale cohort studies are being conducted to test the effectiveness of vaccinations against dementia. Some of them have shown significant results, establishing a statistically significant relationship between vaccinations and a reduction in symptomatology in already diagnosed dementia patients. These vaccines offer lower-cost, low-risk mechanism of prevention of dementia with better outcomes than pre-existing vaccines. However, there is a need of more large-scale retrospective studies and randomized trials, with longer follow-ups, to be conducted to assess the safety and consistent efficacy of this strategy.

The World Alzheimer's Report, published in 2015, estimates that 46.8 million people worldwide suffer from dementia, which is projected to escalate to 74.7 million by 2030 and 131.5 million by 2050 [1]. Alzheimer's disease (AD) also accounts for most of the cases of dementia and affects approximately 5.4 million Americans. AD is often diagnosed in patients older than 65, and its likelihood increases with every decade thereafter [2]. Women have a greater incidence rate as compared to men and it accounts for 60–80% of cases which makes it the most common cause of dementia. There has been significant impact of AD on the populace, according to official records, there has been drastic increase in deaths by 71% between 2010 and 2013 caused by AD [3]. Additionally, individuals diagnosed with severe AD are prone to being completely dependent on caretakers and suffer debilitating motor impairment and memory loss. On the other hand, patients diagnosed with mild symptoms, have an increased likelihood of functional dependence in some situations including trouble managing finances and routine tasks important for living independently [4]. AD is characterized by extracellular accumulation of senile plaques comprising of amyloid-beta, intracellular aggregates of neurofibrillary tangles (NFTs) which are composed of hyperphosphorylated tau, gliosis, progressive cognitive decline and chronic inflammation, however potential treatments that improve quality of life or treat neurologic impairment to an impactful degree, are still unavailable [5].

Only five treatments have been approved including tacrine,

donepezil, rivastigmine, and galantamine for cognitive symptoms in United States, despite the growing population of patients with AD, amongst which memantine is the most recent one, which was approved decades ago [6]. Multiple treatments have been tested in the past and are still being tested in randomized controlled trials and clinical trials to identify potential and effective treatment strategies, to help treat Alzheimer's in a meaningful way. However, despite all the efforts, there is still a lack of efficacious interventions which can offer long term symptomatic relief. Given the side effects associated with pharmacological interventions, a great interest has been noticed in exploring non-pharmacological treatment plans [7]. However, inconsistent benefits have been observed in treatments including cognitive stimulation and cognitive training [8]. Brain stimulation through various approaches is currently under development. Few techniques such as non-invasive stimulation including, transcranial direct current stimulation (tDCS), and repetitive transcranial magnetic stimulation (rTMS) have shown some significant benefit, although target choice, frequency and modality of stimulation were heterogeneous [9,10]. Long-term efficacy and various parameters of intervention and risk are yet to be established. Another consensus reported that there is insufficient evidence supporting the correlation between modifiable risk factors, pharmacological interventions and dietary supplements and a reduction in symptomatology of already diagnosed patients with AD along with delaying its onset [11].

^{*} Corresponding author. Department of Internal Medicine Dow University of Health Sciences, Baba-e-Urdu Road, Saddar Karachi, Pakistan.

E-mail address: Eman.Ali21@dmc.duhs.edu.pk (E. Ali).

A surprising finding by prior studies includes a reduced risk of dementia, in selected populations, including veterans and patients diagnosed with several medical conditions such as chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) following administration of the influenza vaccination [12,13]. Verreault et al.'s findings demonstrated that Alzheimer's disease (AD) could be prevented by vaccinations against various viruses including influenza [14]. Furthermore, a recent meta-analysis, comprising of an aggregated sample size of almost 300,000 patients, also found that the influenza vaccine has the potential for ameliorating risk of dementia. Over a mean follow up of 9 years, Influenza vaccination mitigated the risk of dementia (RR = 0.97; 95%CI: 0.94–1.00; I² = 99%) suggesting that vaccination may serve as a potential means of combating dementia in an aged population with a mean age of 75 [15]. An important consideration, however, is that some of these studies were limited to small cohorts. Until very recently, a new landmark study established a more reliable profile of association between the influenza vaccine and dementia risk reduction by including almost 1 million participants. It found a significant reduction risk with a Relative Risk of 0.60 (95% CI, 0.59–0.61) and an attributable relative risk of 0.034 (95% CI, 0.033–0.035) of Alzheimer's following influenza vaccination, in a nationwide sample of American adults aged 65 and above [16]. Although, this study had a larger sample size, owing to a limited duration of follow-up time and a retrospective cohort design, perhaps, it is not accurate to ascertain a correlation and causation relationship between vaccination and dementia risk reduction, at least until more studies are conducted.

In conclusion, current evidence suggests that the influenza vaccine could potentially prove to reduce the risk of dementia. However, multiple long term prospective cohort studies and randomized controlled trials with extremely long terms of follow up are required before an unarguable relationship between influenza vaccination and dementia incidence can be established. These vaccines could theoretically offer an inexpensive, low-risk mechanism of prevention of dementia, with much better outcomes than pre-existing vaccines and treatments. Avran S et al.'s [16] study however holds promise and provides optimism. On the contrary, multiple drugs have failed phase 3 trials, not meeting efficacy endpoints, despite the early promise of these drugs. Furthermore, they have their own sets of adverse effects, therefore treatment of the patients remains challenging. Thus, by designing clinical trials in an adaptive and innovative manner, it is possible to capture potential evolution of therapeutic interventions over the complex course of disease progression, with one set of vaccinations appropriate for preclinical AD, another for early-stage AD, and lastly for end-stage AD dementia. As the incidence rate of AD will most likely continue to rise, exploration of practical prevention strategies, including the administration of influenza vaccines could eventually prove to be part of a mainstay of an interception plan. However, in addition to conducting more clinical studies to evaluate the aforementioned relationship between vaccination and dementia risk, the importance of curbing the growing rates of vaccine hesitancy across developed nations and imparting knowledge regarding vaccine safety in a convincing and uncondescending way can not be understated.

Ethical approval

This paper did not involve patients, therefore no ethical approval was required.

Sources of funding

No funding was acquired for this paper.

Author contribution

Eman Ali: conception of the study, drafting of the work, final approval and agreeing to the accuracy of the work. Asim Shaikh: conception of the study, drafting of the work, final approval and agreeing to the accuracy of the work.

Trial Registry number

1. Name of the registry: Not applicable.
2. Unique Identifying number or registration ID: Not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable.

Guarantor

Eman Ali, Asim Shaikh.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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