

Low Dose X-Ray Radiation Can Decrease the Risk of Severe COVID-19 in Individuals with the Alzheimer's Gene

Alireza Mortazavi^{1#}, Bevelacqua JJ^{2#}, Rohit Gosain³, Haghani M^{4*} and SMJ Mortazavi^{5*}

¹School of Medicine, Shiraz University of Medical Sciences, Iran

²Bevelacqua Resources, Richland, USA

³UPMC Hillman Cancer Center, Chautauqua, USA

⁴Department of Radiology, School of Paramedical Sciences, Shiraz University of Medical Sciences, Iran

⁵Department of Medical Physics, School of Medicine, Shiraz University of Medical Sciences, Iran

Abstract

The apolipoprotein E gene is involved in Alzheimer's disease (AD). Individuals with at least one copy of APOE e4 gene are vulnerable to AD. Some studies show an association between Alzheimer's gene and higher risk of severe COVID-19. Oxidative stress plays a key role in COVID-19. Since respiratory viral infections are linked to pathophysiological processes such as cytokine production, inflammation, and cell death, they can be associated with a redox imbalance or oxidative stress. Moreover, Low Dose X-Ray Radiation (LDXR) may play a key role in prevention of Alzheimer's disease through mechanisms such as reducing the oxidative stress. In addition, recent studies indicate that low-moderate dose ionizing radiation (LMDIR) can directly ameliorate neurodegeneration and neuroinflammation. Thus, researchers have suggested that the therapeutic effects of LMDIR in AD might be mediated by its anti-inflammatory and neuroprotective effects. By combining these approaches, we believe that low dose radiation therapy (LDRT) can open new horizons in treatment of the elderly patients with the Alzheimer's gene who suffer from severe pneumonia related to COVID-19. As most victims of the COVID-19 are elderly patients, this issue becomes more important. Clinical trials are underway related to using LDXR alone or in combination with one or more drugs/treatment methods in treating COVID-19. The results of these trials should determine the optimum LDRT parameters that can be beneficial for COVID-19 patients. It can be concluded that LDRT might offer a possible treatment protocol for COVID-19 patients with the Alzheimer's gene who need hospitalization and intensive care.

Keywords: Low Dose X-Ray Radiation (LDXR); Alzheimer's disease; COVID-19; SARS-CoV-2; Coronavirus

Introduction

A growing body of evidence indicates that the apolipoprotein E gene on chromosome 17 (APOE gene) is involved in Alzheimer's disease (AD) [1,2]. There are three polymorphic forms of APOE; namely APOE2, APOE3, and APOE4, while carriers of APOE4 have a higher risk of developing AD [3]. Individuals with at least one copy of APOE e4 gene have a higher risk of developing AD. Having one or two copies of the APOE e4 allele not only increases the risk of late onset AD (~ 3 or 12-fold, respectively), it shifts the age of onset earlier (~ 1-2 decades) [4]. It should be noted that having two copies of APOE e4 genes further increases the risk of getting AD [2]. However, acquiring one or two copies of APOE e4 genes does not correspond to developing AD.

A new study shows that the Alzheimer's gene is associated with higher risk of severe COVID-19 [5]. It has been shown that the APOE e4 allele can raise the risk of severe COVID-19 infection regardless of preexisting diseases (e.g. dementia, cardiovascular disease, and type-2 diabetes). APOE e4 can also alter the lipoprotein function and hence the risk of cardio-metabolic diseases. Moreover, it can moderate the macrophage pro-/anti-inflammatory phenotypes [6]. The mechanism proposed for the effect of APOE e4 on the risk of COVID-19 is based on the link between APOE e4 and ACE2 receptors which play a key role in the spread of the disease "*The novel coronavirus SARS-CoV-2 causing COVID-19 uses the ACE2 receptor for cell entry. ACE2 is highly expressed in type II alveolar cells in the lungs, where ApoE is one of the highly co-expressed genes. Further investigation is needed to understand the biological mechanisms linking ApoE genotypes to COVID-19 severity*" [5].

Moreover, it is known that oxidative stress plays a key role in COVID-19. Since respiratory viral infections are linked to pathophysiological processes such as cytokine production,

inflammation, and cell death, they can be associated with a redox imbalance or oxidative stress [7]. It has previously been reported that low dose x-ray radiation (LDXR) may play a key role in prevention of Alzheimer's disease through multiple mechanisms including reducing the oxidative stress "*Another mechanism, which is possibly involved, is preventing neurodegeneration caused by oxidative stress. It should be noted that oxidative stress is a pathological hallmark of neurodegenerative tauopathies (e.g. AD and PD) [8]. While high doses can induce Reactive Oxygen Species (ROS) formation, oxidative stress and neuroinflammation, substantial evidence now indicates that LDR can mitigate tissue damage through antioxidant defenses [9].*" [10].

Clinical trials are underway (or are recruiting patients) related to using LDXR alone or in combination with one or more drugs/treatment methods in treating COVID-19 [4]. Given this consideration, we should know rather soon in what magnitude LDXR therapy can be beneficial for COVID-19 patients [11,12]. It is worth noting that,

***Corresponding authors:** Haghani M, Department of Radiology, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran, Tel: +989173093013; E-mail: m.haghani4744@yahoo.com

SMJ Mortazavi, Professor, Department of Medical Physics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, Tel: +13234427246; Fax: +98713232-9364; E-mail: mortazavismj@gmail.com

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different protocols are being used by different groups in these trials around the world [13]. We believe that the timing of the radiation exposure after the start of the disease in terminally ill individuals may be critical.

It has recently been shown that low-moderate dose ionizing radiation (LMDIR) can directly ameliorate neurodegeneration and neuroinflammation both *in vivo* and *in vitro*. Based on these findings, researchers have suggested that the therapeutic effects of LMDIR in Alzheimer's disease (AD) might be mediated by its anti-inflammatory and neuroprotective effects [14]. Regarding possible therapeutic effects of LDIR on AD, these researchers state "It has been suggested that possible therapeutic effects of LDIR on AD might be mediated by regeneration of the myelin sheath, inhibition of neurodegeneration by oxidative stress and increase of adult neurogenesis [10]" (Figure 1). Besides stimulation of adult neurogenesis and amelioration of neuroinflammation that seems to be among the most likely mechanisms, the up-regulation of Hsp70 should also be considered. It is worth noting that the potential therapeutic advantages of Hsp70 for the prevention or treatment of AD have been addressed previously by Hoshino et al. [15]. Given these considerations, the relationship between LMDIR and Hsp70 needs further investigation.

Low Dose Radiation Therapy (LDRT) has been successfully used for amyloidosis for several decades [16]. Previous studies showed that

LDRT effectively removes amyloid from various body organs such as the trachea and brain [16]. It is worth noting that in contrast with widely used drug therapies, LDRT to the brain not only removes the amyloid but also results in cognitive improvement [17]. Given these considerations, it can be hypothesized that LDXR can decrease the risk of severe COVID-19 in individuals with the Alzheimer's Gene (Figure 2).

Some early findings provide human evidence that LDXR to the brain, as provided in several normal CT scans, can lead to significant improvements in patients with advanced AD. Cuttler et al. have published a case report about significant improvement in a patient with advanced AD who received 5 brain Computed Tomography (CT) scans. The estimated dose of each scan was about 40 mGy and this dose was received over 3 months [18]. In their second update on the 81-year-old female patient with advanced AD who was treated by LDXR, they reported that at her 83rd birthday, she was able to chew and swallow and appeared relatively happy [19]. Now, a clinical trial entitled "Low Dose Ionizing Radiation Using CT Scans as a Potential Therapy for Alzheimer's Dementia: A Pilot Study (LDIR-CT-AD)" is recruiting patients in Ontario, Canada [20]. The findings of this clinical trial are expected to further determine to what extent LDXR from repeated CT scans can improve function, cognition and behavior in patients with severe AD.

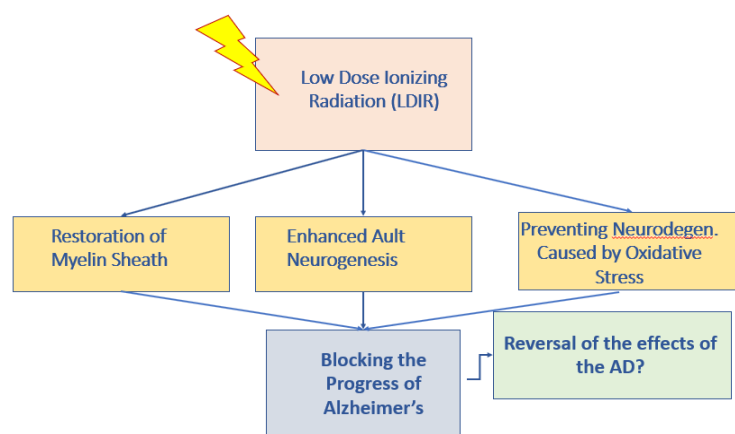


Figure 1: Regeneration of the myelin sheath, inhibition of neurodegeneration by oxidative stress and increase of adult neurogenesis can be introduced as possible therapeutic effects of LDIR on AD. (Figure originally from Bevelacqua and Mortazavi) [10].

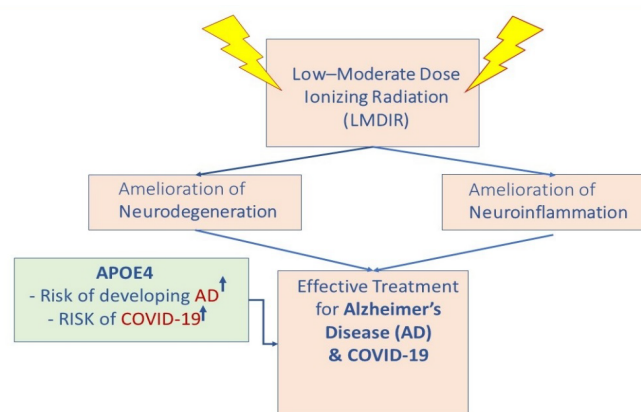


Figure 2: LDXR not only decreases the risk of AD but also it can decrease the risk of severe COVID-19 in individuals with Alzheimer's Gene.

Given this consideration, we believe that LDRT can open new horizons in treatment of the elderly patients with the Alzheimer's gene who suffer from severe pneumonia related to COVID-19. It is worth highlighting that most victims of the COVID-19 are mostly elderly patients [21]. As announced by the Korea Centers for Disease Control and Prevention (KCDC), the mortality rate of COVID-19 patients aged 80 or older is more than 17 percent [22]. Moreover, elderly patients with hypertension, diabetes, and Chronic Kidney Disease (CKD) usually use angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers that upregulate the ACE-2 receptor (the receptor that the SARS-CoV-2 virus uses to enter host cells) [23]. This issue further increases the efficiency of LDRT for elderly patients.

This note suggests the possible beneficial effects of using LDXR to decrease the risk of severe COVID-19 in individuals with the Alzheimer's gene. LDXR offers a possible treatment protocol for individuals with the Alzheimer's gene, and may be particularly beneficial for elderly patients with preexisting conditions.

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