

## CMV Driven Immunosenescence and Alzheimer's Disease

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### Abstract

Cytomegalovirus (CMV) is well known for producing severe life-threatening infection in immunocompromised hosts (HIV, organ transplant). CMV latently infects immune competent individuals as well and has been linked to Alzheimer's disease. Nearly all elderly carry the CMV virus and the immune consequence of CMV can be overwhelming. This article reviews Alzheimer's and its pathology, CMV and immune risk and how the immune dysfunction can lead to Alzheimer's. Early risk detection with new biomarker imaging technology for Alzheimer's along with antiviral drugs and immune support with telomerase activation may all mitigate the expected epidemic of Alzheimer's disease.

**Keywords:** Alzheimer's; Immunosenescence; CMV; Immune risk profile; T-cell inversion; Retinal amyloid; Telomere; Telomerase; Retinal amyloid index

### Introduction

Alzheimer's disease (AD) is the most common cause of dementia with a worldwide prevalence of about 25 million in 2010, and is expected to double by 2030 because of increased life expectancy [1]. The earliest recognizable pathological event in AD is cerebral amyloid- $\beta$  aggregation [2]. This pathology may be present up to 20 years before the onset of dementia [3,4].

The driving force for the AD is disruption of the net balance between production and clearance of aggregated amyloid. The ubiquitin proteasome system (UPS) and autophagy are complementary mechanisms that accomplish important cellular housekeeping functions: removal of protein aggregates, turnover of organelles as well as the elimination of intracellular pathogens [5,6]. Ubiquitin-tagged macromolecules - "cargo" - are delivered to the lysosome by various methods: endocytosis for extracellular elements [7] autophagy for intracellular cargo [8] and phagocytosis and xenophagy for pathogens [9].

Viruses, and CMV specifically, can subvert the UPS to aid their survival [10,11].

When not removed from the cell, amyloid is prone to form aggregates [12,13] and this aggregated amyloid becomes a potent neurotoxin and plays a critical role in the pathogenesis of AD [14,15].

### Immunosenescence

Aging is characterized by a progressive decline of physiologic function and this is markedly manifest in the immune system. Aging results in inadequate initiation and resolution of immune responses - *immunosenescence* - and a chronic low-grade inflammation - *inflammaging* [16]. This chronic, yet subclinical status has been linked to metabolic syndrome, atherosclerosis, cancer and neurodegenerative disease, included AD [17].

Senescent and hyperactive microglia have been detected in the aged and diseased brain [18]. Microglia are the innate immune cells of the central nervous system and are involved in several physiological and pathological brain functions [19,20].

### Cytomegalovirus (CMV)

Chronic and repeated infections promote immunosenescence and inflammaging [21]. Cytomegalovirus (CMV) promotes age-like immune changes [22,23] and CMV reactivation has been associated with increased levels of IL-6 and TNF and premature mortality [24,25].

CMV is part of the herpes family of viruses. CMV is most known as an opportunist causing life-threatening infection in HIV infected persons or immunosuppressed organ transplant recipients. In immune competent individuals, infection with CMV is usually asymptomatic, even in neonates, but once established, its containment becomes a priority for the immune system, which is unable completely to eliminate it. However, even healthy immune competent people may display symptoms of CMV infection more often than previously appreciated [26], sometimes even with serious consequences and with age implicated as a risk factor [27]. The consequences to the immune system for maintaining this constant CMV vigilance may be severe. Reports on the very young and the very old show that CMV infection results in similar alterations to CD8+ T cell subset surface phenotypes [28,29]. This has given rise to the concept that what are apparent age-associated changes could rather be due to age-associated increases in prevalence of CMV infection. This suggests an overwhelming impact of CMV on the aging T cell immune system [29].

The persistent presence of CMV diverts an extraordinary amount of the T-cell resource to keep this virus in check and in doing so results in a high immune risk profile (IRP) inverting the normal CD4/CD8 ratio. The clonally expanded CD8 cell population carrying receptors for the CMV antigen are dysfunctional cells. This is consistent with the suggestion that these cells contribute to the pro-inflammatory state seen in the elderly thought to contribute to frailty and mortality [30,31]. In the elderly positive for CMV there is paucity of naïve T-cells and an accumulation of terminal T-cells with no proliferative capacity and with short telomeres [32].

CMV has been implicated as a causal agent in AD [33,34]

### Telomeres and telomerase

Telomeres are highly conserved repetitive DNA sequences that undergo shortening with each cell division (reflecting cellular replicative history) [35,36]. Telomere shortening with concurrent cell senescence,

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Received November 24, 2015; Accepted November 25, 2015; Published November 30, 2015

Citation: Dow CT (2015) CMV Driven Immunosenescence and Alzheimer's Disease. J Neuroinfect Dis 6: 195. doi:10.4172/2314-7326.1000195

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oxidative stress, and aging are important factors in the pathogenesis of AD [37] and can also negatively influence telomere length [38-40]. Telomere length in T-cells of AD patients is shown to correlate with disease status, suggesting systemic immune system alterations in AD pathogenesis [41].

Up regulation of the enzyme telomerase, to add telomeres, is proposed as a potential strategy for aging and AD because overexpression of TERT can protect neurons from amyloid induced apoptosis [42-49].

Amyloid aggregates play an important role in the inhibition of telomerase activity; the amyloid oligomers bind to telomeric DNA/RNA hybrids. More and more studies have demonstrated that soluble oligomers of amyloid are active species that ultimately cause neuronal damage as well as the synaptic loss and dementia associated with AD [50-52].

While cellular senescence is generally considered to result from critical telomere attrition [53], this loss can be restored by the enzyme telomerase [54,55]. Telomerase is a reverse transcriptase with an intrinsic RNA template that produces new telomeric DNA; telomere erosion reflects the sum of the telomere loss and telomere restoration by telomerase [55,56].

## Discussion – Is There an Opportunity to Treat AD?

The seminal Swedish OCTO and NONA immune longitudinal studies identified and confirmed an immune risk profile predictive of high 2-year mortality in elderly individuals – 86 to 94 years old. This immune profile was associated with persistent cytomegalovirus infection and characterized by an inverted CD4/CD8 ratio caused by expansion of terminally differentiated T-cells [57]. Interestingly, an extension of the NONA study looked at those study participants who reached 100 years of age. The results confirmed high IRP was a major predictor of mortality in this population of the very old and suggests that survival to the age of 100 years is associated with the maintenance of a low IRP [58]. The testing strategies were further used to test a younger group - 66 years old. Termed the Swedish HEXA study, the findings of inverted CD4/CD8 ratio and associated CMV seropositivity, similar to those of the very old, were found in 15% of that population suggesting that the high risk immune profile (IRP) seen commonly in the very old already exists in some who are 20 years younger than very elderly [59].

Preventing or delaying infection would be an obvious first line strategy and prophylactic vaccination would be additive. However, for those already infected, reducing viral load with drugs is another option, and new approaches in AIDS and transplant patients are resulting in the development of improved antiviral agents with fewer side effects, such as ganciclovir, valganciclovir, foscarnet, or cidofovir. These drugs are now being used extensively, with a reasonable safety record, which could suggest use in the elderly [60].

By up-regulation of telomerase, an enzyme that adds telomeres, old cells can be “rescued” from senescence. A small molecule compound isolated from the *Astragalus membranaceus* plant is capable of up-regulating telomerase activity [61]. This was identified in an empirical screen of traditional Chinese medicine plant extracts and compounds having reported properties of health maintenance and enhanced immune function.

A new imaging technology that will allow earlier detection of amyloid is currently under study. It involves simple imaging for amyloid in the retina of the eye. As the retina is an extension of the brain and amyloid deposits are seen in pathologic sections of the retina, new imaging technology has been developed that can not only show the amyloid

but can quantify it: assigning a number, the retinal amyloid index. The retinal amyloid deposition mimics and correlates with amyloid of the brain [62]. This exciting technology may detect the risk for AD years or even decades before dementia giving an opportunity to make lifestyle changes and study drugs at an early juncture where they may have more impact. Additionally, determination of the immune risk profile (IRP) particularly as it relates to CMV will allow opportunities to support the immune system and “treat” prodromal AD.

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**Citation:** Dow CT (2015) CMV Driven Immunosenescence and Alzheimer's Disease. *J Neuroinfect Dis* 6: 195. doi:[10.4172/2314-7326.1000195](https://doi.org/10.4172/2314-7326.1000195)