Impact of frailty on depression

Background

With increasing life expectancy, diseases associated with old age have increased in growing proportion in recent decades. (1) The integration of frailty measures in clinical practice is crucial for the development of interventions against age-related conditions (in particular, disability) in older persons. Multiple instruments have been developed over the last years in order to capture this geriatric ‘ multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors’ and render it objectively measurable. (2) Frailty is not uncommon to the medical contemporary research nowadays. Several possible definitions were given by different researchers in the past to define frailty. One and commonly used definition of physical frailty was given by Fried et al, Frailty was defined as a clinical syndrome in which three or more of the following criteria were present; unintentional weight loss (10lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. (3) Frailty in older people was again classified into prefrail – those having one or two criteria given by Fried et al, and frail elderly – having three or more criteria as per Fried et al definition. Medical Syndrome like frailty, keeps older adults at increased risk of adverse health outcomes when exposed to a stressor. (4) Stressors lead to decline across multiple physiological systems incrementally and are associated with greater depressive symptoms and disability. (5)

Depression is not a normal part of ageing process (6) and is a potentially life-threatening disorder that affects hundreds of millions of people across the world. (7) Depression is commonly seen in frail older people as they may

face widowhood or loss of function or independence or bereavement. Depression, if left untreated, complicates other chronic conditions such as heart disease, diabetes, stroke, etc. It may also incur health care costs and often accompanies functional impairment and disability. (6) Various systematic reviews and journal articles has demonstrated association between depression and frailty. In this review, focus has made to highlight the role of stressors that leads pathways linking depression and frailty.

Prevalence of frailty, depression and their co-occurrence in older individuals

Several studies have been carried out to measure the prevalence of frailty in community-dwelling older people as well as those in hospital settings. Majority of the studies have used similar criteria to measure frailty among older adults. Systematic review of frailty prevalence worldwide concluded that 10. 7% of community-dwelling adults aged â‰¥65 years were frail and 41. 6% pre-frail. (8) It was noted that prevalence figures varied substantially between studies (ranging from 4% to 59%) using different criteria to measure frailty. (6) Data from Survey of Health, Aging and Retirement in Europe (SHARE) in 2004 covering more than 10 European countries, showed prevalence of frailty and pre-frailty in 65+ age group as 17. 0% (15. 3 – 18. 7) were frail and 42. 3% (40. 5 – 44. 1) were pre-frail. (9) The prevalence of frailty in community dwelling older people ranged from 17%-31% in Brazil, 15% in Mexico, 5%-31% in China, and 21%-44% in Russia. However, prevalence of frailty was again found much higher in institutionalized older patients as 32% in India and 49% in Brazil. Findings of study in outpatient clinics reported prevalence of frailty was 55-71% in Brazil and 28% in Peru.

(10) Above finding suggests that older people of low- and middle-income countries were found frail in significant proportions which imply policy and health care provisions for this ageing population.

Depression varies in its prevalence in different studies and settings. Prevalence of depressive symptoms was found 14% in Brazilian adults (11), 9% in United State's general population (12) and 23. 6% (95% CI: 20. 3-27. 2%) in Chinese older adults. (13) Depressive symptoms were most commonly associated with women (11) (12) (13) and single adults (i. e. divorced, unmarried or widowed) than in married older adults. (13) Prevalence of depressive illness rises further in the event of associated co-morbid condition such ascancer, diabetes, and hypertension[N1]. Median prevalence of minor depression was 14. 4% and 10. 4%, in medical settings and community-based setting, respectively[N2]. (14) The median global prevalence of serious depression in the elderly population is around 1% – 5%. (15) (16) (17)

Depressed elders show many phenotypical expressions of frailty and vice versa. Coexistence of both depression and frailty among older people has been investigated in several studies. (18) (19) (20) (21) (22) (23) A recent systematic review examined the relationship between depression and frailty found serious depression in 4 – 16% of frail individuals who are aged 60 and over. (6) However, this percentage rises to 35% in older population with age 75 years or more. (6) (24) A study conducted within framework of prospective cohort study, the Netherlands Study of Depression in Older Persons (NESDO) found that the prevalence of physical frailty was significantly higher in the depressed group in comparison with non-

depressed (27. 2% vs 9. 1%, p <0. 001). (18) Logistic regression analysis showed an increase odds ratio of frailty for depression (OR= 2. 66, 95% CI: 1. 36-5. 24, p= 0. 004) after adjusting other co-variates such as age, gender and all baseline characteristics. Another study conducted in Mexican older population also found clinically evident depressive symptoms in 22. 7% of older frail (25), whereas study conducted on 2, 488 older population of Toledo, Spain observed prevalence of frailty 8. 4% in 65+ years, increased to 27. 3% in older than 84 years and depression (Geriatric depression scale> 4) was present in as high as 46. 5% of the frail subjects. Depressed patients often exhibit symptoms that interfere with their ability to function normally for longer duration which facilitates progression of frailty syndrome. (6) Therefore, in order to improve health and preventing frailty & depression in elderly, it is essential for researchers and practitioners to understand the linking phenomena for further research and developing treatment options.

Main pathways linking frailty and depression

Several studies have identified the possible physiological pathways that link between frailty and depression in older adults. Of which, the main hypothetical pathways identified were vascular depression, chronic inflammation, Hypothalamus-Pituitary-Adrenal (HPA) axis dysregulation and accelerated cellular ageing.

Vascular depression hypothesis

Alexopoulos et al.(26) proposed that “ cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes.” This statement was supported by another study of vascular depression based on magnetic resonance imaging (MRI) conducted by

Krishnan KR et al. (27). Bivariate analyses and a fully adjusted logistic regression model in MRI study revealed that older age, late age at onset, and nonpsychotic subtype occurred more often in patients with vascular depression than in those with nonvascular depression. He also observed that anhedonia and functional disability were seen somewhat more often in patients with vascular depression.

There are several clinical studies that examined vascular disease in depression. Some studies (28) found a highly significant increase in physical illness and vascular risk factors in the late onset group, after adjusting for age when they compared early and late onset late-life depression. (29) On the other hand, several others found no association of depression with cerebrovascular score (30) and vascular disease (31). Depression may occur as a result of vascular disease in a significant subpopulation of elderly persons. (32) Depression has a bidirectional association with vascular diseases and plausible mechanisms exist which explain how depression might increase these vascular diseases and vice versa. Thomas AJ et al summarized that coronary artery disease (CAD) and stroke are all associated with high rates of depression and depression is an independent risk factor for the subsequent development of CAD and stroke. (29)

Mechanism of vascular depression can be hypothesized as reduced cerebral blood flow (CBF) in response to given stressors. Normal CBF in adult humans is about 60ml/100 grams/min and regionally, about 70ml/100g/min in gray matter and 20ml/100g/min in white matter. Between the ages of 20 to 65, normal CBF generally declines about 15-20%. It is generally accepted that when CBF reaches 30ml/100g/min, neurologic symptoms can appear and

when CBF falls to 15-20ml/100g/min, electrical failure or irreversible neuronal damage can occur even within minutes. (33) Blood flow to the brain is influenced by systemic hemodynamics and cerebro-vascular auto-regulation, with cerebral arteries contracting or dilating as arterial pressure changes. These processes interact to maintain stable perfusion. (33) However, these processes are impaired in the context of vascular disease: hypertension, diabetes, and atherosclerosis lead to vascular wall hypertrophy, reduced arterial lumen diameter, reduced arterial distensibility, and endothelial cell dysfunction. This affects cerebral blood flow.

Mild CBF reduction may impair cognitive and affective processes, while greater CBF reduction may cause ischemic injury. The subcortical white matter is particularly sensitive to these changes because it is supplied by terminal arterioles with limited collateral flow and so susceptible to infarction due to impaired autoregulation. Greater white matter hyperintensities (WMH) severity may be a marker of broader deficits in perfusion and autoregulation. Thus, risk factors for vascular disease can lead to subclinical cerebrovascular disease throughout the brain.

Katz (2004) theorizes that cerebrovascular disease that causes prefrontal white-matter hyperintensities and vascular depression may also lead to posterior white matter hyperintensities, resulting in characteristics of frailty such as falls, slowness, and weakness. (34) He further stated that if the effects are anterior, the manifestations may include depression. However, if the effects are more posterior, the manifestations may be in the form of disturbances of gait and balance. Several other studies had compared depressed elderly with control group and demonstrated an increase in deep

white matter hyperintensities (DWMH) in depression (35) (36) (37), but no or not significant association with peripheral vascular lesion (PVH) (36) (37). The cerebral WM contains fiber pathways that convey axons linking cerebral cortical areas with each other and with subcortical structures, facilitating the distributed neural circuits that subserve sensorimotor function, intellect, and emotion. The vascular depression hypothesis postulates that altered mood regulation and cognitive dysfunction in the elderly are due to subclinical cerebrovascular ischemia that disrupts frontostriatal neural circuits. (38) (39) This disruption of fronto-striatal neural circuits leads to disconnection syndrome that corresponds to the clinical and neuropsychological profile of LLD. (40) Prefrontal WMH also leads to executive dysfunction which affects planning, self-monitoring, attention, response inhibition, co-ordination of complex cognition (as in Trail making Test) and motor control. This leads to frailty.

Chronic Inflammation hypothesis

Aging- and disease-related processes promote proinflammatory states in older individuals. Administration of cytokines or induction of peripheral inflammation results in an inflammatory response, which in turn is correlated with fatigue, slowed reaction time, and mood reduction. Even without medical illness, depressed individuals exhibit increased levels of proinflammatory cytokines and reduced anti-inflammatory cytokine levels.

Proinflammatory cytokines affect monoamine neurotransmitter pathways, including indoleamine 2, 3-dioxygenase upregulation and kynurenine pathway activation. This results in decreased tryptophan and serotonin and increased synthesis of detrimental tryptophan catabolites that promote

hippocampal damage and apoptosis. Cytokines, including IL-1Î², also reduce extracellular serotonin levels by activating the serotonin transporter.

Effects of the CNS inflammatory cascade on neural plasticity

Microglias are primary recipients of peripheral inflammatory signals that reach the brain.

Activated microglia, in turn, initiate an inflammatory cascade whereby release of relevant cytokines, chemokines, inflammatory mediators, and reactive nitrogen and oxygen species (RNS and ROS, respectively) induces mutual activation of astroglia, thereby amplifying inflammatory signals within the CNS.

Cytokines, including IL-1, IL-6, and TNF-alpha, as well as IFN-alpha and IFN-gamma (from T cells), induce the enzyme, IDO, which breaks down TRP, the primary precursor of 5-HT (serotonin), into QUIN (quinolinic acid), a potent NMDA (*N* -methyl-D-aspartate) agonist and stimulator of GLU (glutamate) release.

Astrocytic functions are compromised due to excessive exposure to cytokines, QUIN, and RNS/ROS, ultimately leading to impaired glutamate reuptake, and increased glutamate release, as well as decreased production of neurotrophic factors.

Of note, oligodendroglia are especially sensitive to the CNS inflammatory cascade and suffer damage due to overexposure to cytokines such as TNF-alpha, which has a direct toxic effect on these cells, potentially contributing to apoptosis and demyelination.

The confluence of excessive astrocytic glutamate release, its inadequate reuptake by astrocytes and oligodendroglia, activation of NMDA receptors by QUIN, increased glutamate binding and activation of extrasynaptic NMDA receptors (accessible to glutamate released from glial elements and associated with inhibition of BDNF (brain-derived neurotrophic factor) expression), decline in neurotrophic support, and oxidative stress ultimately disrupt neural plasticity through excitotoxicity and apoptosis.

- 5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; GLU, glutamate; IDO, indolamine 2, 3 dioxygenase; IFN, interferon; IL, interleukin; NMDA, *N*-methyl-D-aspartate; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRP, tryptophan.

Regarding LLD, the aging process disrupts immune function, increasing peripheral immune activity and shifting the CNS into a proinflammatory state. Elevated peripheral cytokine levels are associated with depressive symptoms in older adults, with the most consistent finding being for IL-6, but also implicating IL-1Î², IL-8 and TNFÎ±.

Proinflammatory states in older adults are associated with cognitive deficits, including poorer executive function, poorer memory performance, worse global cognition, and steeper decline in cognition. Finally, greater IL-6 and C-reactive protein levels are associated with greater WMH burden.

In LLD, ischemic lesions are also more likely to occur in the dorsolateral prefrontal cortex (DLPFC), Similarly, depressed elders exhibit increased expression of cellular adhesion molecules (CAMs) in the DLPFC. CAMs are

inflammatory markers whose expression is increased by ischemia, supporting a role for ischemia in LLD and highlighting the relationship between vascular and inflammatory processes.

HPA dysregulation

When the HPA axis is activated by stressors, such as an immune response, high levels of glucocorticoids are released into the body and suppress immune response by inhibiting the expression of proinflammatory cytokines (e. g. IL-1, TNF alpha, andIFN gamma) and increasing the levels of anti-inflammatory cytokines (e. g. IL-4, IL-10, andIL-13) in immune cells, such as monocytes and neutrophils.

Excess stress also appears to play a role in the development of depression and can cause dysregulation of the HPA axis. Patients with major depression have been found to have elevated plasma and urinary cortisol levels as well as elevated corticotropin-releasing hormone and decreased levels of BDNF.

Prolonged severe stress is thought to damage hippocampal neurons and to reduce the inhibitory control exerted by the HPA axis in regulating glucocorticoid levels.

During an immune response, proinflammatory cytokines (e. g. IL-1) are released into peripheral circulatory system and can pass through the blood brain barrier where they can interact with the brain and activate HPA axis. Interactions between the proinflammatory cytokines and the brain can alter the metabolic activity of neurotransmitters and cause symptoms such as fatigue, depression, and mood changes.

Increased levels of aldosterone in the circulation stimulate excessive production of collagen, which leads to fibrosis of tissue or organ whereas low levels of adrenal androgen dehydroepiandrosterone sulfate and insulin-like growth factor 1 are associated with frailty. Further, cortisol may mimic the effects of aldosterone. Elevated serum levels of cortisol and aldosterone are independent predictors of mortality in patients with heart failure.

Accelerated Cellular Aging hypothesis

Accelerated cellular aging, as measured by telomere length (TL) shortening, might also be linked to depression and frailty.

At both ends of every DNA strand in a human cell is a telomere. Telomeres prevent chromosomes from becoming frayed, fusing into rings, or binding with other DNA.

Telomeres are specialized nucleoprotein structures located at the end of eukaryotic chromosomes. They play a critical role in controlling cell proliferation and maintenance of chromosomal stability.

As part of body’s normal aging process, each time a cell divides the telomeres in your DNA get shorter. Add oxidative stress to the mix and telomeres shorten even more rapidly. Oxidative stress is the effect of destructive reactions in your body’s cells caused by too many free radicals or atoms/molecules that have unpaired electrons. In their search for an electron to make them whole, they destroy other cells. Free radicals come from environmental toxins, such as pollution, chemicals, drugs and radiation, and even naturally occur in your own body when you exercise. Antioxidants fight free radicals and stem the causes of oxidative stress.

Eventually, body’s cells are unable to divide (or reproduce) and simply die. Eventually, this instability leads to tissue breakdown potentially leading to premature aging.

Any stressful condition or anxiety leads to feeling of depression which in turn initiates physiologic body response that includes, increase in stress-induced glucocorticoid release and oxidative stress. Unhealthy behaviour will also stimulate inflammatory response which lead to release of cytokine and can affect telomere length.