Review paper

Immunosenescence and late life depression

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Abstract

Late life depression is highly prevalent disease which violently affects health and shortens life span. WHO expects depression to become the first leading cause of disease burden by the year 2030. There are evidences from depressed people including elderly that oxidative damage and immune-inflammatory activation play a role in depression and there is a need or extensive studies on links between this biological systems. The problem of how depression is related to immune system in elderly is complicated, as immune system shows many age-dependent changes and there is a growing body of data concerning the complex process of immunosenescence. Main alteration in immune functions in aging concern low-grade inflammatory activity and altered acute phase response, level of T cells and neutrophils functions. There is evidence that systemic inflammation is related to local pathology in the CNS and in consequence alter neuroplastic processes and lead to depression. There is also evidence that brain-endocrine-immune response in successful aging is correlated with metallothioneines (MTs) and therefore homeostasis of zinc. Aging significantly disturbs the functional role of MTs leading to zinc deficiency. Decreased level of zinc , even within the reference values, affects activity of antioxidant zinc-dependent enzymes, multiple aspects of innate and adaptive immunity and psychological dimensions in elderly.

Key words: *late-life depression, oxidative stress, low grade inflammation, immunosenescence, zinc, metallothioneines.*

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Introduction

Late-life depression has been defined as occurrence of depressive symptoms in people at age over 65 (International Statistical Classification of Diseases and Related Health Problems. 10th Revision. World Health Organization). There is some evidence that the prevalence of depressive symptoms increase with age and that most of depressed people do not receive medical treatment for their psychiatric conditions [1-2]. Depression violently affects health and shortens life span due to increased risk of cardiovascular events [3-15]. Immune response alterations and hypothalamic-pituitary-adrenocortical axis hyperactivity, have been suggested to cause cardiovascular pathology in depressed subjects [16]. Depression is also a predictor for mortality from cancer, respiratory diseases, neuropathologies, metabolic diseases and mental disorders [17-23]. Presence of one or more chronic physical diseases increases significantly the risk of comorbid depression. Comorbidity leads to health worsening compared with depression alone as well as chronic diseases alone and with any combination of them without depression [24]. Depressed patients represent lower health status than patients without depression [25-27]. The problem of depression has been shown in World Health Organization predictions. WHO expects depression to become the firs leading cause of disease burden by the year 2030, advancing from the second position in the former prognoses for 2020 [28-29]. There is a need for the extensive studies on mechanism involved in ethiopatogenesis of late-life depression to combat the growing medical, social and economic problem and successfully cure depression.

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Oxidative damage and immune-inflammatory activation play a role in depression

There are evidences from depressed people including elderly that oxidative damage and immune-inflammatory activation play a role in depression and there is a need or extensive studies on links between this biological systems [30-33]. It has been reported that proinflammatory cytokines i.e. IL-1, IL-6, TNF-α enhance oxidative damages of DNA, expressed as increase of 8OH-dG [34- 35]. One of the theories proposed for aging is the Oxidative Theory of Aging [36]. Although this theory was put forth in 1956 and was widely supported [37-40], as well as relationship between systemic oxidative stress and unsuccessful aging [41], the role of free radicals in ethiopatogenesis of late-life depression had not been investigated for the long time. Even in the half 90s there were evidences for oxidative stress contribution in many diseases but authors did not mentioned depression [42-43]. Moreover only in 2006 there were first data on oxidative damage to DNA in clinical depression [44].

Much more research have been conducted to understand relation between depression and immune functions. The problem of how depression is related to immune system in elderly is complicated as immune system shows many age-dependent changes and there is a growing body of data concerning the complex process of immunosenescence.

Aging related low-grade inflammatory activity

Aging is associated with chronic, low-grade inflammatory activity and altered acute phase response [45-46]. In elderly subjects cytokine production shifts from Th1 to Th2. Interelukin IL-2 and interferon INF-gamma production decreases and IL-4 and IL-10 increases [47-51]. The balance between proinflammatory and anti-inflammatory cytokines response are crucial for successful aging. Increased production of proinflammatory cytokines and chemokines have been observed in healthy aged subjects as well as in old people with developed pathologies in most studies [45, 52-54]. Pro-inflammatory cytokines, TNF-α and IL-1β induce a second wave of cytokines including chemokines and IL-6 and further induces the synthesis of acute phase proteins [46].

Although elevated level of circulating inflammatory mediators was confirmed in age-related diseases the nature of direct role of inflammatory mediators remains to be unclear with indications on a positive feedback mechanism causing direct pathogenetic role of TNF-α and IL-6 [55]. Circulating level of TNF-α and IL-6 in elderly differs depending on progress of inflammatory diseases, and TNF-α is a marker of frailty in the very elderly whereas IL-6 do not affect survival in centenarians [56-57]. Increased soluble tumor necrosis factor receptor sTNF-R observed in the serum of elderly people may oppose the physiologic effects of TNF [58]. It has been hypothesized that association of an increased serum level of IL-8 and low level of IL-6 is related to longevity [59].

Inflammatory mediators in late-life depression

Increase in IL-1β, IL-6 and TNF-α has been reported in late-life depression [33, 60-63]. In regard to IL-1β, a high innate IL-1 receptor antagonist (IL-1ra) to IL-1β production capacity results in better ability to neutralize inflammation, have protective effect against depressive symptoms in elderly. Conversely low IL-1ra and high IL-1β productions add up to risk to develop depression via modulation of the HPA-axis activity and serotonin re-uptake stimulation. The question whether these cytokines originate from microglia cells in the brain or from the systemic inflammatory response, needs further research [63].

Immune functions in elderly

Increased level of serum immunoglobulins G, M and A [49-50, 52], alpha 2-macroglobulin [49] and memory T cells [49, 64] has been observed in elderly. On the contrary level of lymphocytes, T cells [49-50] and the titers of zinc [50] have decreased. Number of T cells decreases and the CD8 cells decreased more than the CD4 cells, resulting in a increased CD4/CD 8 ratio. Moreover, lower number of naive (CD45RA+) and a higher number of memory (CD45R0+) were observed [49-50]. Decrease in number of B cells and specific antibodies is coupled with increase of unspecific immunoglobulins [49-50].

The main changes observed in neutrophils are increased activation coupled with diminished phagocytic capacity, depressed oxidative burst, reduction in chemotaxis and resistance in apoptosis [47, 50]. Higher number of neutrophils and monocytes has also been observed in depressed elderly [33].

Natural killer cell activity is also deteriorated with age and defects in their functional activity can be linked with decreased production of IL-8 and decreased production of superoxide in granulocytes [47, 50, 52, 65-66]. Late –life depression is associated with impaired peripheral immune efficiency [67].

Monocytes, basophils, eosinophils remain unchanged during aging [49-50]. C-reactive protein(CRP) has been also reported not age dependent [49, 68].

The relations of CRP to depression in general population has not been established however high concentration of CRP has been demonstrated in association with depressive symptoms in elderly people [63, 69-70].

Systemic inflammation and CNS function

There are evidences that systemic inflammation is related to local pathology in the CNS due to cytokines crossing the deteriorated blood-brain barrier and activation of hypothalamic-pituitary-adrenal axis [71-72]. Increased release of corticotropin-releasing hormones (CRH) in hypothalamic and extrahypothalamic sites may influence

serotonin (5-HT) processes, and in consequence alter neuroplastic processes and lead to depression [73]. It has been also hypothesized that peripheral inflammation represents spillover from inflammatory processes in CNS [45]. Communication between peripheral immune activation and the brain is mediated by IL-1β, IL-6 and TNF-α [63, 74].

Brain-endocrine-immune response and zinc status in relation to depression

Altered immune response due to its interrelationship to brain and endocrine system can affect their functions which are pivotal for development of depressive symptoms. There are evidences that brain-endocrine-immune response in successful aging is correlated with metallothioneines (MTs) and therefore homeostasis of zinc. Zinc deficiency, even within the reference values, affects activity of antioxidant zinc-dependent enzymes, multiple aspects of innate and adaptive immunity and psychological dimensions in elderly [50, 75-80]. Immunomodulatory and antidepressant-like effect of zinc suplementation has been also confirmed [81-83].

MTs are induced by IL-6 and glucocorticoids to protect cells from reactive oxygen species and induce prompt immune response. Aging significantly disturbs this process as the functional role of MTs turn-off from dispensing to sequesting zinc due to constant inflammation and chronic oxidative stress. Increased level of MTmRNA in lymphocytes of elderly subject in comparison with young-adults and nonagenarians has been reported. In old mice high level of liver MTmRNA goes together with increased level of IL-6 and glucocorticoids, depressed IL-2, decreased NK cell activity and impaired capacity of poly(ADP-ribose) polymerasse-1 (PARP-1), low level of zinc ions bioavailability and loss of immune plasticity. Zinc deprivation and aging bear many similarities in immune functions alterations [50, 75, 79, 84-86].

Immune activation in late life depression has been also confirmed with data suggesting increased level of pterins in depressed elderly subject [87].

There is significant set of scientific data to describe changes in immune system during ageing but there is need for the extensive studies on immunosenescence in relation to oxidative stress and further on the links between immune dysregulation and oxidative stress in clinical depression [88].

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