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Neuroinflammatory mechanisms of delirium in elderly

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Νευροφλεγμονώδεις μηχανισμοί στο ντελίριο των ηλικιωμένων

Περίληψη στο τέλος του άρθρου

Key words: Cytokines, Delirium, Elderly, Neuroinflammation

INTRODUCTION

Delirium in elderly patients of general hospitals is an acute condition that disrupts their attention and cognitive function, and manifests in a short period of time.[1] Considered the *sine qua non* of psychiatric disorders in general hospitals, delirium not only is the most common psychiatric diagnosis for consultation-liaison psychiatrists, but also a medical emergency due to its morbidity and mortality.[2] It is the most frequent complication in elderly inpatients and may also be the sole manifestation of a serious underlying disease.[1] Many mechanisms contribute to delirium manifestation. Among these, neuroinflammatory processes possibly possess a central role: inflammation in periphery activates the innate immune system and leads to the inflammatory process which results to delirium.[3]

NEUROINFLAMMATORY MECHANISMS OF DELIRIUM IN ELDERLY

Delirium may accompany many medical and surgical conditions that are related to increased inflammatory response: sepsis-related multi-organ failure, infections or postoperative states.[4] Infections trigger the production and circulation of factors such as interleukins, TNF-α and heat shock proteins.[5] These inflammatory mediators pass the blood-brain barrier (BBB) and induce damage to neurons and synapses. Disruption of the BBB is believed to cause the neuroinflammatory process.[3]

Nevertheless, the exact mechanisms through which inflammation in periphery disrupts brain function are not fully elucidated and many findings are based on experimental models.[6] The peripheral immune system has a great impact on brain, and many proinflammatory cytokines communicate with the brain through various mechanisms, such as neuronal pathways or entrance through the BBB. The hypothesis of brain immunological privilege is no longer considered to be true, and studies show that there is a continuous bidirectional communication between central nervous system (CNS) and peripheral immune system.[7]

During acute infections or trauma, the brain coordinates a central response through activation of the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic and the parasympathetic nervous system.[8] Reaction to stress begins from the hippocampus and the hypothalamus, and, through the autonomic nervous system and the pituitary, leads to increased noradrenaline and cortisol secretion from adrenal glands.[9] Thus, the hypothalamus secretes large concentrations of hormones that affect the pituitary, and consequently the adrenal glands, which secrete adrenocorticotropic hormone in order to minimize the levels of stress induced by the inflammatory process. Chronic, high levels of cortisol contribute to important processes at the neurotransmitter level possibly resulting to delirium effects.[10]

The neuroinflammatory hypothesis of delirium is among the most studied.[11] According to this hypothesis, acute inflammatory activation in periphery induces activation of the cells of brain parenchyma, expression of proinflammatory cytokines and inflammatory mediators in the CNS.[12] It is well known that, during threatening situations, such as

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infections or traumatic injuries, immunological reactions are incorporated to the full spectrum of the homeostatic mechanisms of the human organism.[8] The neuroinflammatory process is currently recognized widely as a chronic process contrary to systemic infections, which may be acute or chronic.[11]

The disruption of the BBB allows inflammatory cytokines or macrophages from monocytes in the periphery to enter the brain and act on afferent branches of the vagus nerve activating microglial cells and inducing inflammatory response. This results to synaptic dysfunction and neuronal apoptosis affecting the cognitive function in the end.[3]

The human organism activates counter-acting mechanisms in order to restrain the systemic immune response. These mechanisms include anti-inflammatory cytokines, stress hormones and signals from the CNS, which altogether cause release of acetylcholine from the vagus nerve that interacts with nicotinic cholinergic receptors in immune cells.[13]

The increased inflammatory response may lead to upregulation of indoleamine dioxygenase and addition of neurotoxic metabolites from the tryptophan-kynurenine pathway. The increase of neuroinflammatory cytokines causes an important change in tryptophan metabolism toward the production of metabolites from the kynurenine pathway; these have biological functions that may lead to cytotoxicity, apoptosis and neuronal cell.[11]

INFLAMMATORY BIOMARKERS OF DELIRIUM IN ELDERLY

Cytokines

Cytokines are usually found in extracellular space and at low levels in the CNS. But stress, infections and trauma increase the release of cytokines leading to activation of the hypothalamic-pituitary-adrenal (HPA) axis, increased permeability of the BBB and disordered synthesis and transmission of neurotransmitters.[14] Acute systemic infections are related to changes in cognitive function due to disordered molecular and cellular functions in various brain areas, especially hippocampus.[15]

The neuroinflammatory process in delirium, which causes memory and learning deficits, is related to decreased expression of the brain-derived growth factor in hippocampus, increased oxidative stress and mitochondrial dysfunction, elimination of neurotrophic and increase of local proinflammatory cytokines. Inflammation, apoptosis and necrosis are possible outcomes of the disruption of homeostasis and TNF-α may be a biomarker of these processes.[16] Reactive oxygen species in the brain, proinflammatory cytokines, metalloproteinases, nitrous oxide and chemokines may disrupt the functions of learning and memory affecting the synaptic plasticity and the processes of long-term potentiation.[17] According to a hypothesis, in the healthy brain the production of cytokines may have just a few deleterious effects but may strengthen neurodegenerative processes when a neuronal damage already exists.[14]

The release of cytokines and other neuroinflammatory mediators decreases the oxygenation and leads to decreased brain oxidative metabolism. The inflammatory mediators due to the systemic infection, combined with the increased permeability of the BBB which causes neuronal and synaptic dysfunction, activate microglial and other adjacent cells causing the cognitive and behavioral symptoms of delirium.[12]

C-reactive protein

C-reactive protein (CRP) may trigger the creation of reactive oxygen species. Systemic infections increase the CRP levels and disrupt the function of the BBB, causing neuroinflammation and clinical manifestation of delirium. Higher levels of CRP have been related to increased incidence of delirium, which might be indicative of the role inflammatory processes may have.[18]

Endogenous opioids

The endogenous opioid system is activated under stress conditions. The opioids meperidine and morphine are related to postoperative delirium, even though this may be a result of their anticholinergic side-effects. Endothecal administration of beta-endorphins and disorders of circadian rhythms of beta-endorphins and cortisol may also be related to delirium.[19]

Cortisol

Cortisol plays an important role in the stress reaction of the human organism. The response of cortisol to stress and its duration are increased in elderly people and in neurodegenerative conditions, such as dementia.[20] Exaggerated secretion of cortisol has toxic effects in mood and memory and the hippocampus is a principal target of these effects due to the dense concentration of glucocorticoid receptors.[18]

Studies of patients with delirium have shown that cortisol is increased both in blood and cerebrospinal fluid.[21] The

increased secretion of glucocorticoids inhibits the transfer of glucose to the neurons and consequently leads to energy deficit, which especially impairs the hippocampus and causes cellular death through various mechanisms.[18]

Activation of the HPA axis and increased levels of corticosteroids are implicated in cognitive dysfunction. Cortisol regulates the activity of the limbic system and this may explain some of the cognitive disorders in elderly with delirium.[14] Thus, there exists an age-related dysregulation of the HPA axis resulting in easier response to stress. Taking these facts into consideration, it is not surprising that delirium is frequently seen in acute stress conditions with increased cortisol levels.[20]

Oxidative stress

Increased passage of kynurenine through the BBB strengthens delirium through oxidative stress. Oxidative stress leads to influx of Ca^{2+} ions in the nervous cell, mitochondrial dysfunction and protein stress response.[22] Decreased oxygen supply to the brain causes deficient oxidative metabolism which causes brain dysfunction. The physiologic process of aging also decreases the function of organs affecting oxygen supply.[18]

Activation of the clotting mechanism

Inflammation may also contribute to delirium manifestation through activation of the clotting mechanism, as is the case in sepsis and COVID-19 infection. Hypercoagulability states are related to decreased levels of protein C or increased levels of D-dimers and may cause effects that vary from disorders of brain self-regulation to thrombosis and ischemia.[6]

Microglia

Microglial activation may play an important role in innate immunological reaction of the brain since it may lead to the production of inflammatory mediators. These mediators may further cause modification of immunological actions and affect neuronal function. Disrupted neuronal function is possibly the last step that causes clinically significant behavioral changes as a result of systemic infection. Release of proinflammatory factors from microglial cells causes a vicious cycle of neuroinflammation and the release of cytotoxic substances may cause acute, reversible behavioral effects (such as those seen in patients with delirium). Activation of microglial cells increases the levels of protein S100β, a marker of neuronal damage and a prognostic factor of the duration of delirium.[7] Microglial cells are activated through various routes. Activated microglial cells are quickly transformed to a proinflammatory phenotype and strengthen the production of proinflammatory molecules.[3]

Epigenetics

Epigenetics refers to changes in gene expression caused by histone modification and DNA methylation. It seems to play a crucial role in synaptic plasticity, learning and memory, as well as the disruption of the function of the BBB.[3]

SYNOPSIS

Delirium is a common and serious complication of acute medical conditions in elderly patients and is associated with high morbidity and mortality. Neuroinflammation seems to play a central role in the pathophysiology of the syndrome and inflammatory biomarkers could aid toward elucidating the underlying pathophysiologic process.

ΠΕΡΙΛΗΨΗ

Νευροφλεγμονώδεις μηχανισμοί στο ντελίριο των ηλικιωμένων

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Το ντελίριο (delirium) είναι η πιο συχνή επιπλοκή που παρουσιάζουν ηλικιωμένοι νοσηλευόμενοι ασθενείς και όχι μόνο αποτελεί τη συχνότερη ψυχιατρική διάγνωση για τους ψυχιάτρους στις υπηρεσίες συμβουλευτικής-διασυνδετικής Ψυχιατρικής αλλά και μια ιατρικώς επείγουσα κατάσταση λόγω της νοσηρότητας και της θνητότητάς της. Πολλοί μηχανισμοί συμβάλλουν στην εκδήλωση delirium, με τις νευροφλεγμονώδεις διεργασίες να κατέχουν ενδεχομένως κεντρική θέση: η φλεγμονή στην περιφέρεια ενεργοποιεί το ενδογενές ανοσιακό σύστημα, διεγείρει την παραγωγή και την κυκλοφορία παραγόντων, όπως οι ιντερλευκίνες, ο TNF-α και οι πρωτεΐνες θερμικού shock, και παρέχει γένεση στη φλεγμονώδη διεργασία που οδηγεί στην εκδήλωση delirium. Αυτοί οι φλεγμονώδεις διαμεσολαβητές διαπερνούν τον αιματοεγκεφαλικό φραγμό και επάγουν βλάβη σε νευρώνες και συνάψεις. Η διατάραξη του αιματοεγκεφα-

λικού φραγμού πιστεύεται ότι προκαλεί τη νευροφλεγμονώδη διεργασία. Η αποσαφήνιση του υποκείμενου μηχανισμού πρόκλησης του delirium θα μπορούσε να οδηγήσει σε καλύτερες στρατηγικές πρόληψης και θεραπευτικής διαχείρισης αυτών των ασθενών, ενώ φλεγμονώδεις βιοδείκτες, όπως η CRP, θα μπορούσαν ίσως να συνδράμουν προς αυτή την κατεύθυνση.

Λέξεις ευρετηρίου: Ηλικιωμένοι, Κυτταροκίνες, Νευροφλεγμονή, Ντελίριο

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