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Proposed Mechanisms for Cancer- and Treatment-Related Cognitive Changes

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Abstract

Objectives—To review the proposed mechanisms of cognitive changes associated with non-central nervous system cancers and cancer treatment.

Data Sources—Review and synthesis of data-based publications and review articles.

Conclusion—Proposed mechanisms include cytokine upregulation, hormonal changes, neurotransmitter dysregulation, attentional fatigue, genetic predisposition, and comorbid symptoms.

Implications for Nursing Practice—Oncology nurses need to understand the multiple mechanisms that may contribute to the development of cancer- and treatment-related cognitive changes so that they can identify patients at high risk and can help patients understand why these changes occur.

Keywords

cognition; *cancer*; *cytokines*; *inflammation*; *neurotransmitters*

A patient's cognitive function is important for navigating treatment, maintaining social support, and accomplishing meaningful goals during and following cancer treatment.[1] However, attention and other components of cognitive function (e.g., working memory, information processing speed) may be impaired as a result of cognitive changes directly associated with cancer treatment or other clinical factors in patients with non-central nervous system (CNS) cancers.

Cancer- and treatment-related cognitive changes may be mediated through inflammatory cytokine upregulation and hormonal changes.[2] In addition, the biology of the cancer,[3] as

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well as stress[4] and attentional fatigue[5] may contribute to cognitive changes. Finally, genetic predisposition[2] and co-occurring symptoms[6] may explain some of the inter-individual variability in these cognitive changes. The severity of cognitive changes may be moderated by age.[7]

The purpose of this article is to review the evidence for various mechanisms that may underlie the development of diminished cognitive function in patients with cancer and cancer survivors (see Figure 1). However, relevant findings in other populations and from pre-clinical studies are included. The article concludes with a discussion of clinical implications and recommendations for future research.

Treatment-Related Mechanisms

Evidence suggests that cancer treatments play a role in cognitive changes. Chemotherapy is the most frequently evaluated treatment for its effects on cognitive function.[8] Some chemotherapeutic drugs cross the blood-brain barrier (e.g., carmustine) or may be administered intrathecally (e.g., methotrexate), potentially damaging the CNS directly.[2] High-dose chemotherapy may cause more damage to the CNS than standard-dose chemotherapy.[9] In addition, treatment-induced cardiotoxicity may impact cognitive function by reducing the flow of blood to the brain.[2] Alternatively, systemic chemotherapy may induce CNS damage through inflammatory pathways upregulated by non-apoptotic cell death.[10]

Other treatments may contribute to cognitive changes. Surgery[11] and radiation therapy[12] may result in cognitive changes through peripheral tissue damage that activates inflammatory pathways. In addition, anesthesia administered during surgery could impact cognitive function directly.[13] Finally, hormonal therapy could influence cognition through changes in hormone levels.[14]

Cytokine Upregulation

Peripheral inflammation may mediate cognitive changes associated with cancer treatment.[10] A peripheral inflammatory state can be communicated to the CNS in many ways (e.g., through afferent nerves such as the vagus nerve[15,16]). In response, proinflammatory cytokines are produced by microglial cells in the CNS.[15] These central cytokines damage neurons by inducing oxidative stress.[17] Therefore, peripheral inflammation may negatively impact cognitive function.[18]

Chemotherapy drugs may damage the CNS indirectly through the production of free radicals (e.g., reactive oxygen species).[2,19] When cellular antioxidants are unable to neutralize free radicals, cells enter a state of oxidative stress in which cellular structures and DNA are damaged.[19,20] Mitochondria, which produce cellular energy, are susceptible to oxidative damage because of their involvement with free radical production and their poor DNA repair capabilities.[19,21] Damage to mitochondria may reduce neuronal energy production, leading to poorly functioning neurons.[19,22] Damaged or poorly functioning neurons may be destroyed by apoptosis, contributing to cognitive changes.[23]

Results of one study demonstrated that administration of doxorubicin, which is not known to cross the blood-brain barrier,[19,24] was associated with increased levels of the proinflammatory cytokine tumor necrosis factor-alpha in the periphery.[25] This upregulation of peripheral cytokine levels may be communicated to the CNS, subsequently damaging neurons via oxidative stress.[2,18,26]

Study results suggest that upregulated peripheral cytokine levels and peripheral oxidative stress mirror oxidative stress in the CNS. Researchers conducting pre-clinical studies found that mice treated with doxorubicin had higher levels of CNS neuronal oxidation.[17,27] Similarly, in a recent study of breast cancer survivors an average of six years after chemotherapy, oxidative DNA damage in peripheral white blood cells was associated with decreased grey matter density in the brain.[28] These findings support the pathway whereby treatments that do not pass the blood-brain barrier can damage CNS neurons indirectly. The possibility exists that DNA damage induced by inflammation contributes to further immune activation, potentially perpetuating a cycle of DNA damage and inflammation.[2]

Although damage to CNS neurons may explain partially the cognitive changes patients experience, neural progenitor cells and neuroglial cells also are important. Neural progenitor cells replenish damaged neurons and neuroglia in the hippocampus.[29] These cells are active in building neural tissue in the hippocampus, which is responsible for consolidation of short-term memories.[29] If the pool of neural progenitor cells is decreased due to treatment-induced toxicity, the CNS has less ability to repair damaged neurons and maintain hippocampal tissue.[29] In addition, damage to oligodendrocytes, a type of neuroglial cell, impairs myelination of white matter tracts, thereby reducing processing speed.[30]

Results from pre-clinical studies using mouse models indicated that systemic chemotherapy damages lineage-restricted neural progenitor cells and oligodendrocytes.[29,31] After chemotherapy administration, neuronal cell death continued at an increased rate for at least six weeks,[29] and white matter tracts remained impaired for at least six months.[31] Taken together, injury to neural progenitor cells and oligodendrocytes partially may explain long-term and delayed cognitive changes experienced by cancer survivors, particularly changes in memory and processing speed.[29]

Hormonal Changes

Estrogen—Estrogen is important for verbal memory[14] and learning.[32] The hormone increases production of acetylcholine, which is important for memory.[14] Estrogen promotes the development of synapses in areas of the brain involved in memory, such as the hippocampus.[33] In addition, the hormone is important for neuronal cell growth and maintenance.[34] Decreases in estrogen levels may occur because of systemic chemotherapeutic agents, which can damage hormone-producing tissue, or as a result of anti-estrogen therapy.[14] Anti-estrogen therapies include aromatase inhibitors, which block the conversion of androgens to estrogen, and selective estrogen receptor modulators (e.g., tamoxifen).[32] These treatments are used to prevent the recurrence of hormone-sensitive tumors.[32]

Treatment-induced menopause may occur in pre-menopausal women undergoing systemic treatment.[14] Women who experience the precipitous decline in estrogen levels that occurs as a result of treatment-induced menopause, as opposed to the more gradual hormonal changes that occur with natural menopause, may report more pronounced cognitive changes. Moreover, because estrogen is thought to be neuroprotective,[34] women who enter treatment-induced menopause earlier in life may be at greater risk for more severe cognitive changes.[14]

Testosterone—Testosterone is important for cognitive function, particularly for visuospatial ability[35] and working memory,[36,37] as well as the maintenance of synaptic density in the hippocampus.[38] Administration of testosterone is associated with elevated mood and cognitive function. In contrast, low levels of the hormone are associated with deficits in neurotransmission, fatigue, poor mood, and worse cognitive function.[39]

Administration of testosterone to men with Alzheimer's disease or mild cognitive impairment has been shown to improve cognitive function.[40]

Androgen deprivation therapy (ADT) is used to prevent growth of hormone-sensitive prostate cancer.[41] ADT severely reduces testosterone levels, which may impact cognitive function in subtle but meaningful ways for patients.[37] Because aromatase converts testosterone to estrogen, blocking testosterone lowers estrogen levels.[42] Therefore, some of the cognitive changes these men experience may be related to estrogen deprivation.[35,37]

Findings from clinical studies about the effects of ADT are mixed. In one recent study of men post radiation therapy, no significant differences were found in the cognitive functioning of men who received ADT compared to men who did not.[43] Another recent study[44] was conducted to explore this relationship using functional magnetic resonance imaging. Men treated with ADT showed decreased activity in cortical structures important for top-down cognitive control compared to men not treated with ADT, although both groups performed similarly on objective tests of cognitive function. Therefore, imaging may be more sensitive to treatment-induced cognitive changes than objective tests.[44]

Other Clinical Factors

In a number of recent studies, cognitive changes were found in patients before adjuvant treatment for cancer. For example, researchers found worse verbal memory and attention in women before adjuvant treatment for breast cancer compared to women without breast cancer.[45] Although the effects of surgery may account for these findings,[11,45] other clinical factors may explain cognitive changes before treatment.

Tumor-associated macrophages release proinflammatory cytokines that alter the micro-environment surrounding the tumor.[3] This alteration promotes an environment that is hospitable to growth and metastasis.[3] Tumor-induced inflammatory changes could contribute to a chronic inflammatory state before treatment, which may affect cognitive function through the same mechanisms attributed to treatment-induced inflammation.[10] Comorbidities may impact cognitive function directly (e.g., heart failure).[46] Moreover, management of multiple comorbidities may strain the cognitive systems of the brain.[47]

The high, sustained levels of stress experienced by patients after diagnosis of cancer could contribute to cognitive changes. The allostatic load hypothesis suggests that physical and psychological stressors impact common biological pathways to produce cognitive changes via cytokine upregulation.[4,10,48,49] Through the process of allostasis, the body adjusts to stress by adaptations.[46] However, chronic stress may tip these adjustments into allostatic overload, negatively impacting cognitive function through dysregulation of immune function.[46]

Attentional fatigue is an important contributor to cognitive changes.[1] Three networks are thought to compose the attention system of the brain: the alerting, orienting, and executive networks.[50] Together, these networks allow for normal attentional function. Of particular importance to attentional fatigue is the executive network, which is responsible for synthesizing conflicting input from separate brain areas into a coherent response. This “effortful control”[50] is experienced in part as making rational decisions, planning to meet goals, monitoring the self during social interactions, and controlling the expression of emotions.

The pervasive distractions that oncology patients experience after diagnosis can lead to reduced ability to continue to exert effortful control[50] (i.e., attentional fatigue[51]). Because effortful control has high metabolic demands and its effectiveness is sensitive to variations

in glucose levels, short-term attentional fatigue may be mediated by depletion of glucose.[52] However, long-term attentional fatigue can be experienced as burn-out that is not dependent on glucose levels.[53]

In one study, patients who more recently completed chemotherapy or received higher doses of chemotherapy had a significantly lower cerebral glucose metabolic rate than patients who completed treatment earlier, received lower doses of chemotherapy drugs, or received no chemotherapy.[54] Using positron emission tomography, the frontal lobes were shown to have the most severe reductions in glucose metabolism. This impairment pattern parallels age-related changes in cerebral glucose metabolism, which may occur due to an accumulation of neuronal damage due to oxidative stress and mitochondrial dysfunction.[54–56] Support for this hypothesis was found in high levels of oxidative DNA damage in peripheral lymphocytes after chemotherapy treatment in women with breast cancer,[57] as well as higher mutation rates in the mitochondrial DNA of cancer patients.[58] Changes in glucose metabolism may contribute to uncontrolled glucose levels and insulin resistance, which in turn contribute to inflammatory cytokine production, oxidative stress, and hypothalamic-pituitary-adrenal (HPA) axis disruption.[59]

Inter-Individual Differences

Inter-individual differences in cognitive changes before and during cancer treatment and into survivorship may be due to multiple mechanisms that confer susceptibility to, or protection from, cognitive changes. These mechanisms include genetic variations and co-occurring symptoms (e.g., affective symptoms, sleep disturbance).[2] In addition, the severity of cognitive changes may be moderated by age.[1]

Genetic Variations

Inflammatory cytokines—Variations in genes that encode for pro- and anti-inflammatory cytokines partially may explain inter-individual differences in cognitive function among oncology patients.[2] For example, researchers recently found an association between IL6 rs1800795 and level of self-reported attentional function.[60] In that study, each additional copy the rare “G” allele conferred increased odds of belonging to a subgroup of participants with lower attentional function. In another recent study, this allele was associated with memory complaints among women with breast cancer.[61] The G allele is associated with elevated peripheral levels of interleukin-6[62] and inflammation that may contribute to cognitive changes.[63]

Neurotransmitters—The neurotransmitters norepinephrine, acetylcholine, and dopamine are important for cognitive function.[64] Therefore, variations in genes that encode for adrenergic, cholinergic, and dopaminergic pathways may contribute to inter-individual variability in cognitive function.[65] For example, candidate genes that encode for the dopaminergic pathway important to the executive attention network include catechol-O-methyltransferase (COMT), dopamine transporter (DAT1), dopamine receptor D4 (DRD4), dopamine beta-hydroxylase (DBH), and monoamine oxidase A (MAOA).[50,65,66] Likely because of its involvement in dopamine metabolism,[67] COMT is associated with conflict resolution, a function of the executive attention network thought to be dependent on the anterior cingulate cortex (ACC).[50]

In one study, each additional copy of the “Val” allele in COMT rs4680 was associated with greater activity in the ACC and poorer performance on an attentional task.[68] The effect was most pronounced during the most difficult attentional tasks that required the highest level of conflict resolution. The Val allele is associated with faster dopamine metabolism,[69,70] which suggests that this relationship may exist because of less dopamine available to the executive

attention network.[50] This finding is consistent with less efficient operation of the ACC due to reduced dopamine availability.[68] In a study of 130 women treated for breast cancer compared to non-cancer controls,[71] carriers of the Val allele performed significantly worse on tests of attention regardless of cancer history. In addition, women treated with chemotherapy who were carriers of the Val allele performed significantly worse than healthy controls on these tests.

In summary, variations in genes that encode for neurotransmitters may account for some of the inter-individual variability in cognitive function reported by oncology patients. These effects are mediated partially through changes in the efficiency of inter-neuronal communication in attention networks.[65]

Other variants—The epsilon 4 (ε4) allele in the gene that encodes for apolipoprotein E (APOE) is associated with cognitive decline in other populations, notably patients with Alzheimer's disease.[72] Carriers of the APOE ε4 allele are at higher risk for cognitive decline, perhaps through susceptibility to neuronal damage.[72] A study of the effects of this allele in survivors of breast cancer or lymphoma found associations with changes in visual memory and spatial ability.[73]

Variation in genes that encode for DNA repair mechanisms may impact the efficiency of DNA repair.[2] Because decreased efficiency of DNA repair may contribute to cytokine-induced neuronal damage,[2] future studies should determine whether these variants contribute to cancer and treatment-related cognitive changes.

Co-Occurring Symptoms

Affective symptoms—Affective symptoms may explain some of the variability in cognitive function. Difficulty concentrating is a depressive symptom.[74] Psychosocial stressors may contribute to dysregulation of the HPA axis.[6] This dysregulation results in subsequent changes in serotonin metabolism, negatively impacting cognitive control in frontal brain structures that depend on serotonin.[6] In particular, dysregulation of serotonin metabolism in the dorsolateral prefrontal cortex may reduce attentional control of emotional responses.[75] Evidence supporting this hypothesis includes reduction in serotonergic activity in the rat prefrontal cortex[76] and downregulation of serotonin receptors[77] during chronic stress. In addition, because estrogen is important for serotonin production and function,[78,79] anti-estrogen treatments may contribute to this relationship.

Deficits in attentional control may contribute to affective symptoms, given that the ACC exerts control over limbic brain structures involved with emotion (e.g., the amygdala).[50,80] In particular, diminished attentional function may contribute to depressive symptoms.[6] The orienting network of the attention system enables disengagement from some stimuli in order to focus on others.[64] Persons with diminished attentional function may be less able to change the focus of their attention from negative to positive thoughts.[6] Moreover, persons may have an attentional bias toward thoughts with negative emotional connotations and ruminate on these thoughts, which predisposes them to prolongation of negative affect and risk for depression.[6,81,82]

Anxiety was found to be associated with diminished self-reported attentional function in a sample of breast and prostate cancer patients.[83] As state anxiety increases, concentration may be more difficult.[84] Changes in attention may contribute to state anxiety, particularly among individuals for whom the ability to concentrate is highly valued (e.g., individuals whose work is mentally demanding).[85] In addition, high trait anxiety may be a surrogate for neuroticism.[86] Individuals high in neuroticism may be more likely to report changes in attentional function because of their tendency to focus on subtle internal changes.[87]

Recent findings suggest that genetic variations may influence affective symptoms through changes in the efficiency of the executive attention network.[50] For example, carriers of the short allele of a 44-base-pair variable number tandem repeat (5HTTLPR) in the promoter region of a serotonin transport gene (SLC6A4) reported worse anxiety.[88] The short allele is associated with three-fold lower gene transcription, which results in lower levels of serotonin transporter production.[89] These results were linked to decreased ACC control of the amygdala[90] and increased sensitivity of the amygdala to stimuli.[91] While this relationship has not been evaluated in oncology patients, results of a recent study indicated that reduction of serotonin levels through acute tryptophan depletion was associated with diminished verbal memory and psychomotor ability.[92]

Studies reporting a relationship between higher levels of anxiety[47] and/or depressive symptoms[5,84,93–97] with diminished self-reported attentional function support the hypothesis that these symptoms share a common etiology. In addition, attentional function and affective symptoms are influenced by common molecular mechanisms. For example, variations in 5HTTLPR may contribute to anxiety, depressive symptoms, and diminished attentional function through a reduction in executive control of the amygdala.[90] Therefore, variations in genes that encode for serotonin pathways may account for some of the inter-individual differences in attentional function experienced by oncology patients.[90]

Sleep disturbance—The suprachiasmatic nucleus controls multiple circadian rhythm clocks in the brain.[98] Disruption of these physiological clocks can have detrimental cognitive effects. For example, in a recent study of women with breast cancer, higher levels of sleep disturbance were associated with lower levels of self-reported attentional function.[99] Changes in circadian rhythms due to sleep disturbance may negatively impact cognitive function through disruption of neurotransmitter production.[98] Furthermore, the importance of neurotransmitters to brain health in general, including emotional health, may link findings of impaired attentional function and increased levels of affective symptoms. Support for these hypotheses was found in intervention studies in patients with psychiatric or neurodegenerative disease that showed improved cognition and affective symptoms with improved sleep quality.[98]

Age—Younger patients report worse cognitive changes than older patients.[1] However, older patients perform worse than younger patients on neuropsychological tests.[95] These differences may be explained by younger patients noticing more subtle cognitive changes due to the impact on work or home life.[1] In contrast, older patients may have adapted to previous cognitive changes that allow them not to worry as much about cognitive changes associated with cancer and its treatment.[1]

An interesting hypothesis is that treatment for cancer may accelerate the aging process.[7] Specifically, cognitive changes associated with treatment may parallel age-related changes and occur earlier for oncology patients than for age-matched controls (i.e., diminished cognitive function compared to population norms at the same age due to an initial insult to the CNS from treatment).

Implications

While progress has been made in understanding mechanisms of cancer and treatment-related cognitive changes, uncertainty remains for what causes these changes. Moreover, clinicians cannot accurately predict the severity of cognitive changes patients will experience so that patient education and interventions can be targeted. For now, oncology nurses need to understand the mechanisms that contribute to cognitive changes so that they can identify

high-risk patients and explain to patients the reasons for these changes. In addition, the treatment of co-occurring affective symptoms and sleep disturbance is important.[83]

Three important areas for future research are: (1) elucidation of mechanisms, (2) determination of factors that increase susceptibility to cognitive changes, and (3) interventions to prevent or reduce cognitive changes. Results of genetic studies provide information about hypothetical mechanisms by showing associations among cognitive changes and genetic variation.[100] However, the mechanisms underlying these associations are poorly understood. Animal studies may bolster our understanding of the genetic associations found in humans. In addition, the emerging synergy in combining the disciplines of symptom research, immunology, genetics, neuropsychology, and imaging may provide strong evidence for the hypothesized mechanisms of cognitive changes reported by oncology patients.[101] Determination of risk factors will allow clinicians to target education and interventions appropriately. While additional research on underlying mechanisms and risk factors is warranted, the information available today can be used to develop and test interventions to improve this important clinical problem.

Conclusion

The focus of this review was the potential mechanisms that underlie diminished cognitive function reported by oncology patients. In summary, multiple mechanisms may contribute to diminished cognitive function in patients with non-CNS cancers. In particular, cancer- and treatment-related cognitive changes may be mediated through inflammatory cytokine upregulation and hormonal changes.[2] Other clinical factors including the biology of cancer,[3] stress,[4] and attentional fatigue[5] may contribute to cognitive changes. In addition, genetic predisposition[2] and co-occurring symptoms[6] may explain some of the inter-individual variability in these cognitive changes. Potential underlying mechanisms include variations in candidate genes involved in the regulation of inflammatory cytokines and neurotransmitters. The severity of cognitive changes may be moderated by age.[7]

The diagnosis and treatment of cancer may amplify the impact of underlying cytokine dysregulation through induction of chronic peripheral inflammation.[2] The distracting environment associated with cancer treatments may negatively impact cognitive function through attentional fatigue.[1] In addition, sleep disturbance may amplify the negative effects of neurotransmitter dysregulation through disruption of circadian rhythms.[98] Affective symptoms may impact cognitive function directly or share common underlying mechanisms, such as reduced ACC control of the amygdala.[90]

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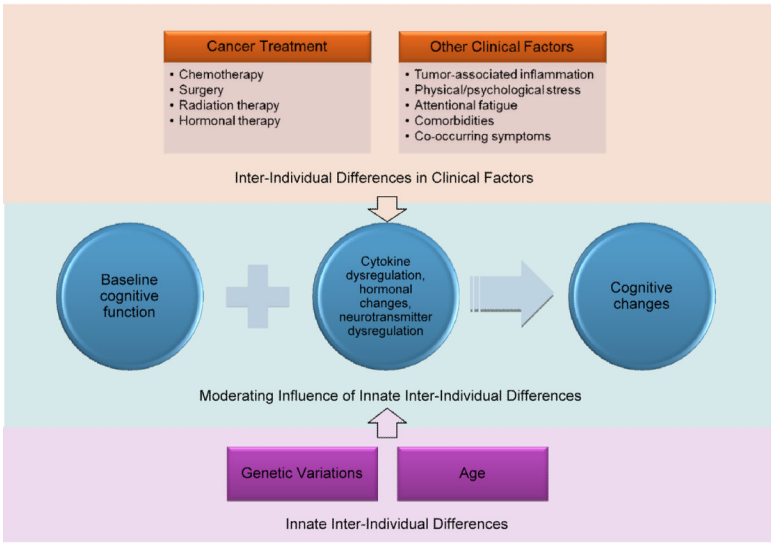

Figure 1.

Proposed Mechanisms for Cancer and Treatment-Related Cognitive Changes. Clinical factors impact baseline cognitive function to produce cognitive changes. These changes may be mediated by upregulation of inflammation, hormonal changes, and neurotransmitter dysregulation. Innate inter-individual differences moderate cognitive changes. The effects of clinical factors and innate inter-individual differences on the mechanisms producing cognitive changes overlap and interact.