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The importance of the Brain Derived Neurotropic Factor in Maintaining Brain Health during and after Cancer Treatments

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Abstract:

Due to the scientific advances of the last decades, cancer patient's survival has greatly improved, and 70% of the patients now live more than five years. However, many of the cancer survivors are affected by a constellation of chronic conditions induced by the powerful cancer treatments required to achieve cancer control. The effects of chemotherapy and radiation therapy on the brain are multifactorial and involve acute and sustained insult to neuronal structures essential for normal cognitive processes as well as for emotional modulation. As result, the cognitive and emotional deficits associated with cancer treatments are pervasive. The Brain Derived Neurotrophic Factor (BDNF) is an important neuromediator that plays a significant role in developing cancer related central nervous system complications. Multiple pharmacological strategies have been proven beneficial in raising BDNF levels. Equally important, there are safe and easy to implement dietary and life-style modifications that physicians can recommend, and which can potentially stimulate BDNF synthesis and improve cancer patient's cognitive and emotional function and quality of life.

Rezumat:

Datorita multiplelor descoperiri stiintifice din ultimele decade, supravietuirea pacientilor cu cancer a crescut semnificativ - 70% din pacientii diagnosticati cu cancer traiesc mai mult de cinci ani. Cu toate acestea, multi pacienti oncologici sunt afectati de o constelatie de conditii cronice cauzate de tratamentele folosite pentru controlul cancerului. Efectele citostaticelor si al radioterapiei pentru tumorile cerebrale sunt multiple si cauzeaza numeroase efecte adverse la nivelul structurilor neuronale necesare pentru memoriei si modularea emotionala. Din acest motiv deficientele de memorie si problemele emotionale sunt observate frecvent. BDNF este un neuromodulator essential, cu un rol foarte important in dezvoltarea complicatiilor la nivelul sistemului nervos central. Interventiile farmacologice s-au demonstrat benefice pentru cresterea nivelului de BDNF. De asemenea, modificari in alimentatie si ale stilului de viata pot fi recomandate de medici si sunt relativ usor de implementat, dar au potential important de a imbunatati memoria, emotiile si calitatea vietii in pacientii cu cancer.

Article:

Due to the scientific advances of the last decades, cancer patient's survival has greatly improved, and 70% of the patients now live more than five years (National Cancer Institute, US). However, many of the cancer survivors are affected by a constellation of chronic conditions induced by the powerful cancer treatments required to achieve cancer control. Numerous deficits – such as limb amputations, hair loss or cardiac damage – are easy to identify and to quantify. However, the burden of hidden conditions – such as cognitive and emotional deficits remains difficult to acknowledge and hard to measure using objective outcomes.

The effects of chemotherapy and radiation therapy on the brain are multifactorial and involve acute and sustained insult to neuronal structures essential for learning and memory as well as for emotional modulation.¹⁻⁸ As a result, the cognitive deficits associated with cancer treatments are pervasive, and 15-50% of patients reportedly develop deficits in memory, attention and executive function (Table 1).⁹⁻¹³ Mood disorders (depression, anxiety) are also extremely common in cancer patients, with the incidence of depression reaching more than 40% of the assessed patients and the incidence of adjustment disorder was 16%.^{14,15} Even more significant, the cancer patients diagnosed with a mental illness had shorter survival than the patients without psychiatric comorbidities.¹⁵ Quality of life, job attainment and psychosocial outcomes are also decreased in cancer survivors, with many patients reporting forgetfulness and trouble with attention in school/work.^{16,17}

The cognitive and emotional deficits seen in cancer patients and cancer survivors are commonly underdiagnosed due to the traditional focus on “fighting the cancer”. Historically, a variety of neuropsychiatric testing measures have been used to define cognitive abilities in cancer patients in clinical trials, but these batteries are difficult to administer and are not commonly used in the clinical practice.^{9-11,18,19} Computer-based neurocognitive testing is an accessible and objective measure of cognition that, when trended prospectively and longitudinally, can detect and define acute and sub-acute cognitive changes, and which might be easier to implement in oncology practices in the future.²⁰ Advanced imaging can be also used in the future for diagnosing cancer-induced cognitive deficits. Studies using brain MRI techniques suggested that reduced hippocampal volume are found in chemotherapy treated colon cancer patients²¹ and brain tumor patients²², respectively.

Neurotrophins are part of a class of signaling proteins essential for the development, the survival and the normal function of the nervous system.²³ Expression of neurotrophins and their receptors occurs normally during development and in response to stimuli such as tissue injury.^{23,24} One of the most important neurotrophins is the brain derived neurotrophic factor (BDNF). BDNF is a growth factor protein encoded by the *BDNF* gene, broadly expressed in the developing and adult mammalian brain (hippocampus,

cortex, basal forebrain)^{25,26}. BDNF-stimulated intracellular signaling is critical for neuronal survival, morphogenesis, and plasticity²⁷. In hippocampus BDNF stimulates actin signaling in the dendritic spines and regulates dendritic spine integrity²⁸, but is also required for neurogenesis²⁹.

BDNF binds at least two surface receptors (TrkB and LNGFR), which activate multiple intracellular signaling cascades. TrkB (a member of the tyrosine kinase family) is encoded by NTRK2 gene, and its autophosphorylation results from ligand-specific association with BDNF. The BDNF-TrkB pathway plays an important role in short-term memory and neurogenesis. The role of LNGFR (Low-affinity nerve growth factor) is still a topic of active research.³⁰

Roles of BDNF have been implicated in brain aging³¹ as well as in the pathophysiology of brain diseases, including Alzheimer, Parkinson and Huntington disease³². BDNF replacement enhances neurogenesis and sensorimotor function after stroke³³, improves memory performance in animal models of Alzheimer disease³⁴ and restores synaptic plasticity in a mouse model of native Huntington Disease³⁵.

BDNF has been proven to also be involved in the pathogenesis of multiple psychiatric illnesses. Higher BDNF levels protect against depression in the elderly³⁶ and BDNF serum levels can predict the development of depression in stroke patients³⁷. Increased glucocorticoid production caused by stress is directly linked to decreased BDNF production³⁸, which in turn further potentiates the depressive symptoms in mice³⁹. An inverse relation between cortisol and BDNF was also shown in schizophrenia⁴⁰ and post-traumatic stress disorder⁴¹. Lower BDNF levels are constantly found in patients with anxiety disorders⁴², and were recently recognized as a biomarker for obsessive compulsive disorder⁴³.

Our published research has shown that chemotherapy treatment induces BDNF downregulation in cultured hippocampal neurons³. Multiple studies conducted in cancer patients have shown both that BDNF is chronically downregulated in cancer patients⁴⁴, and that the lung cancer patients with the severely decreased BDNF levels after receiving cancer treatments are more prone to cognitive⁴⁵ and mood impairments as well as to decreased response to chemotherapy (ESMO 2016, Yufeng Wu report). In patients with B-cell non-Hodgkin lymphoma serum BDNF levels correlate with their ability to perform accurately on cognitive tasks.⁴⁵ These findings suggest that augmenting BDNF levels through either pharmacological or non-pharmacological approaches can be potentially beneficial for both normal brain function and response to treatment in cancer patients.

Pharmacological approaches to increase BDNF are already available and include the administration of antidepressants as the SSRIs and of ketamine⁴⁶. Furthermore, BDNF activation in the hippocampus is required for the biological activity of the antidepressants in the animal models⁴⁶. New research also suggests that augmentation of BDNF levels in hippocampus can be achieved by administration of positive allosteric modulators of AMPA

receptors (ampakines)⁴⁷ and that ampakine administration can potentially prevent chemotherapy-induced neuronal damage (data not published).

Interventional approaches to both increase BDNF and to treat medication-refractory depression in selected patients include transcranial magnetic stimulation (TMS)⁴⁸ and electroconvulsive therapy (ECT)⁴⁹. rTMS upregulates BDNF as well as improves learning and memory in a preclinical model of vascular dementia⁴⁸, and improves motor function in the affected limb, by activating BDNF processing in stroke patients⁵⁰. A recent meta-analysis showed that ECT treatment in patients with pharmacological treatment-resistant major depressive disorder significantly increases serum/plasma level of BDNF⁵¹. Though many of these interventions were not tested in cancer patients, they are safe and well tolerated in multiple patients' populations and can open new areas of potential research in the immediate future.

Multiple nonpharmacologic interventions are also proven to increase BDNF and to help maintain normal cognitive and emotional functions. Environmental enrichment (the creation of a stimulating environment) is proven to increase BDNF, and in turn to increase synaptic plasticity and cognition that potentially slows or reverses cognitive impairment.^{52,53} Physical exercise also increases the BDNF production and has potential links to improvement in cognitive functions, in young adults⁵⁴ and also in elderly population.⁵⁵ Another potential approach is intermittent fasting, which directly upregulates BDNF expression in the hippocampus, and improves synapse associative interactions that might translate into improved learning and memory⁵⁶.

Nutritional approaches reported to increase BDNF are numerous, and include fish oil⁵⁷, Tualang honey⁵⁸, ketogenic diet⁵⁹, cocoa⁵⁹, high flavonoid fruits and vegetables⁵⁹, soy⁶⁰, coffee⁶¹ and green tea⁶¹.

Conclusions:

BDNF is an important neuromediator that plays a significant role in developing cancer related central nervous system complications. Pharmacological strategies to increase BDNF expression in cancer patients are still under research, though antidepressants, TMS and ECT have proven benefits in raising BDNF levels. Equally important, there are safe and easy to implement dietary and life-style modifications that physicians can recommend, and which can potentially improve cancer patient's cognitive and emotional function and quality of life.

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Table 1: Common symptoms of cancer related cognitive deficits (CRCD, chemo brain)

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| <ul style="list-style-type: none"> ▶ Being unusually disorganized ▶ Confusion ▶ Difficulty concentrating ▶ Difficulty finding the right word ▶ Difficulty learning new skills ▶ Difficulty multitasking ▶ Fatigue ▶ Feeling of mental foggy ▶ Short attention span ▶ Short-term memory problems ▶ Taking longer than usual to complete routine tasks ▶ Trouble with verbal memory, such as remembering a conversation ▶ Trouble with visual memory, such as recalling an image or list of words |
|--|