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Review Article

Chemobrain: A critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy

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ABSTRACT

One consequence of modern cancer therapy is chemotherapy related cognitive dysfunction or "chemobrain", the subjective experience of cognitive deficits at any point during or following chemotherapy. Chemobrain, a well-established clinical syndrome, has become an increasing concern because the number of long-term cancer survivors is growing dramatically. There is strong evidence that correlates changes in peripheral cytokines with the development of chemobrain in commonly used chemotherapeutic drugs for different types of cancer. However, the mechanisms by which these cytokines elicit change in the central nervous system are still unclear. In this review, we hypothesize that the administration of chemotherapy agents initiates a cascade of biological changes, with short-lived alterations in the cytokine milieu inducing persistent epigenetic alterations. These epigenetic changes lead to changes in gene expression, alterations in metabolic activity and neuronal transmission that are responsible for generating the subjective experience of cognition. This speculative but testable hypothesis should help to gain a comprehensive understanding of the mechanism underlying cognitive dysfunction in cancer patients. Such knowledge is critical to identify pharmaceutical targets with the potential to prevent and treat cancer-treatment related cognitive dysfunction and similar disorders.

What is chemobrain?

The development of new chemotherapeutic agents and regimens for cancer therapy has led to a significantly reduced risk of recurrence and a higher survival rate in several types of cancer, particularly in breast cancer. This increase in cancer survivors, however, has led to an increased awareness of the chronic adverse effects of cancer chemotherapeutic agents, including undesirable effects on noncancerous cells secondary to the intended cytoxicity on cancer cells. One consequence of modern cancer therapy is post-chemotherapy related cognitive dysfunction, commonly referred to as "chemobrain" [1]. Cognitive dysfunction is the subjective experience when one has deficits in their cognitive function. Objectively measured cognitive deficits will be referred here as "cognitive impairment". A significant number, estimated between 18% and 78% of breast cancer patients report dyscognition soon after initiating chemotherapy treatment [2,3]. While it is possible that cancer can cause cognitive dysfunction and impairment on its own [4–7], a defining feature of chemobrain is the onset of complaint after treatment initiation, with its corresponding assumption of causality. These symptoms are short-term in the majority of patients but have been reported to persist for months to years in ~35% of patients in disease-free remission [3,8]. The findings from the International Cognitive Workshop suggested that cancer-related cognitive dysfunction may be long-term and has been reported to last 5–10 years after treatments in the cancer survivors [9–11].

While chemobrain is not an uncommon clinical problem, it has been difficult to demonstrate clinically significant cognitive impairment. Repeated studies on the effects of chemotherapy have been unable to demonstrate cognitive impairment after treatment [12–20]. Studies that have shown cognitive impairment, both cross-sectional [21–24] and longitudinal [25–28], demonstrate that the impairment is modest, of unclear clinical significance, and correlates poorly with the severity of the subjective experience of chemobrain. Despite the paucity of evidence for cognitive

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impairment, patients with chemobrain consistently report clinically important cognitive dysfunction that impair their daily function, in particular in regards to attention, concentration, forgetfulness, word-finding, multi-tasking, and organization. The clinical presentation of chemobrain is notable for the discordance between the subjective experience of cognitive dysfunction and objective neuropsychiatric measurements [29].

This discordance between dyscognition and impairment been attributed to a variety of possible methodological causes, including problems with the subjective assessment of symptoms, methodological and sensitivity issues of modern cognitive testing, the difficulty of accurately defining both dyscognition and cognitive impairment [29]. To address these methodological issues, the International Cognition and Cancer Task Force (ICCTF) recommended 3 main tests with suggested clinical cut-points to determine cognitive impairment in patients with cancer and treatment [29,32]. The recommended tests, which measure learning and memory, processing speed, and executive function based on findings of the cognitive effects of chemotherapy on the frontal cortex, are Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination. These tests with the recommended standard deviation cut-points for assessment of cognitive impairment provide adequate sensitivity and psychometric properties to better measure cognitive impairment in patients with cancer and treatments [29,32]. However, it seems likely that the discordance between subjective dyscognition and objective impairment is a defining observation of the nature of chemobrain rather than simply being a measurement artifact.

Another important feature of chemobrain is its common, but not mandatory, relationship to several somatoform symptoms, in particular anxiety, depression and fatigue, and overall health-related decline [33]. The clinical picture of chemobrain is that of a patient developing a distressing and often disabling alteration in their subjective cognitive abilities that is difficult to objectively demonstrate and is temporally related to both the biological and psychological consequences of cancer chemotherapy.

Currently, chemobrain is hypothesized to be the result of neuronal injury with consequent inadequate repair, abnormal brain remodeling, and corresponding neuro-endocrine-immunological changes [34]. Studies have described alterations in the blood–brain barrier that allow increased access of cytotoxic agents to vulnerable neurons. Neuroimaging studies suggest that structural and functional changes in the frontal cortex and related white matter tracts, which are implicated in executive and memory function, correlate with chemobrain. Alterations in these areas have been correlated with subjective and objective change in neurologic function [30,31,35], post-treatment volume loss [36,37], and partial recovery over time [4,37,38]. However, the methodology and small sample sizes of these neuroimaging studies do not demonstrate causality or neuronal injury [39]. Evidence to support that oxidative stress, neural repair, immunologic, and endocrine changes in chemobrain are severely limited. The essential questions underlying the validity of the hypotheses underlying the current chemobrain concept, that of direct causality and neuronal injury, are not answered by the scientific literature to date.

The state of the evidence for chemobrain strongly resembles that which is seen in fibromyalgia and chronic fatigue syndrome. Like chemobrain, patients with these illnesses experience subjective and clinically distressing dyscognition, with attention, concentration, forgetfulness, word-finding, multi-tasking, and organization being the most common complaints. Also like chemobrain, measurements of objective neuropsychologic function frequently fail to demonstrate impairment and what is seen in positive studies is of small clinical magnitude [40–42]. The increased recognition of cognitive symptoms in these disorders has led to their inclusion in diagnostic criteria [43,44]. These illnesses also draw support from neuroimaging studies that commonly show alterations in the structure and function of frontal cortical regions that are passingly similar to those documented in chemobrain [45]. Limited evidence of alterations in oxidative stress, neural repair, immunologic, and endocrine changes have also been reported [46]. Both of these illnesses have disputed causal triggers, such as trauma in fibromyalgia and infection in chronic fatigue syndrome, whose validity is also not answered by the scientific literature to date. The clinical and scientific experience of chemobrain is remarkably similar to the dyscognition reported in fibromyalgia and chronic fatigue syndrome. However, no comparative studies between these dyscognitive states have been performed to date. The implications of this observation are that specific chemotherapeutic-related neurologic injury is not required to create the somatic experience of chemobrain.

The discordance between the severity of subjective experience and that of objective impairment is the hallmark of somatoform illnesses, such as fibromyalgia and chronic fatigue syndrome. A somatoform view of chemobrain would consider it as an atypical yet predictable subjective experience that result from the normal functioning of the brain rather than from an injury. In this way, physiologic factors other than direct neurotoxicity from chemotherapeutic agents are the critical ones in establishing and maintaining chemobrain. Chemotherapy, or the psychological ramifications of cancer treatment, may simply be one of a variety of "triggers" that ultimately lead to dyscognition.

We emphasize that viewing chemobrain as a somatoform illness does not undermine its clinical legitimacy or trivialize the patient suffering that comes with it. All human experiences are psychosomatic ones whose existence is dependent on discoverable physiological mechanisms that are potentially susceptible to therapeutic manipulation. Rather, accepting the possibility that chemobrain is related to that seen in somatoform illness provides a unique opportunity in examining the physiologic underpinnings of these illnesses. Do the biologic alterations that accompany the discrete, medically-induced physiologic stress of chemotherapy "trigger" long-term homeostatic change that is causally responsible for the somatoform experience of chemobrain? The current state of evidence is insufficient to answer this question; the answer would have important ramifications on the causality of all somatoform illness. Here, the authors take the position that such a trigger exists. We hypothesize that acute shifts in cytokines related to chemotherapy administration lead to epigenetic alterations. These epigenetic changes persist after the resolution of the chemotherapy-induced immunologic changes and are primarily responsible for creating and maintaining changes in neuroplasticity that underlie the somatoform experience of chemobrain.

2. The relation of alterations in cytokines to dyscognition

Although several candidate mechanisms have been hypothesized to explain chemobrain, the exact biological pathways remain unknown [3,47]. It is highly unlikely that a single biologic trigger is responsible for the dyscognition observed in cancer patients following chemotherapy. However, it seems likely that cognitive symptoms produced by cancers and cancer treatments may share a common final biological mechanism [3,48,49]. Studies from humans and animal models suggest that several cancer-related symptoms may involve the actions of cytokines. Cytokines, along with their systemic effects, have a role in cancer development, progression [50], and the commonly experienced adverse effects of chemotherapy, such as chemotherapy-induced peripheral neuropathy [48] and cognitive dysfunction [34,51]. Cancer patients who received immunotherapy of IL-2 or interferon-α (IFN-α)