

## Chemobrain - A Troubling Side Effect of Chemotherapy

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### Abstract

**Introduction:** The term chemobrain is a short name for chemotherapy associated cognitive dysfunction. So far there is neither clear definition of the term chemobrain nor its epidemiology or pathogenesis are known and there have been no prospective studies addressing this condition.

**Method:** Here, in this short review we provide an overview on the most recent findings of chemobrain pathogenesis, prevention and available treatment. We take a novel perspective on the role of blood-brain barrier in the development of chemotherapy associated cognitive dysfunction and discuss briefly new and upcoming treatment.

**Results:** The lack of knowledge, information and appropriate diagnostic and monitoring tools is particularly detrimental for elderly patients (>65 years) more susceptible to troublesome and life quality affecting cognitive dysfunctions. In the absence of effective preventive methods, raising awareness and educating patients about possible cognitive dysfunctions as a result of chemotherapy should be implemented.

**Conclusion:** All cancer patients undergoing treatment and experiencing cognitive dysfunctions should be informed about the transient nature of the dysfunction and given options of either pharmacological or cognitive – behavioral therapy aimed at reducing the symptoms.

**Keywords:** Cancer; Chemobrain; Foggy mind; Chemotherapy; Cognitive impairment; Blood brain barrier

### Chemobrain – A Foggy Brain of Cancer Patients

The first mention of the term chemobrain appeared in the literature in response to a steady flow of clinical reports and research articles on neurological dysfunctions and so called “foggy brain” in chemotherapy treated cancer patients [1,2]. “Foggy brain” more precisely known as a cognitive impairment of the brain is a phenomenon with a long history in psychiatry and neurology, however its presence in cancer patients has not been reported until relatively recently. Cognitive impairment as a result of chemotherapy was first mentioned in the 70s but it was not until late 80s when it was clearly recognized. Over years more and more reports were providing solid evidence for a chemotherapy associated cognitive impairment in cancer patients [3,4]. Patients treated with chemotherapeutics were often complaining of visual memory lapses (impaired or delayed recognition of objects, pictures, shapes), verbal difficulties (difficulties with recalling names, concepts, definitions etc) and inability to focus on complex and multi-step tasks. The severity of the symptoms depends on the patient, ranging from mild, almost unnoticeable changes in brain function to severe, highly symptomatic neurological dysfunctions impairing patients’ life [5,6].

Chemobrain is the most prevalent in a population of cancer patients aged 65 years and above. Numerous studies show that the risk of cancer treatment related side effects, including chemobrain, increases with age. This is due not so much as to patients’ chronological age, but rather stems from limited organ reserves, existing comorbidities, polypharmacy, nutritional status, emotional disorders and socioeconomic status of these patients [7,8].

The etiology of these chemotherapy associated cognitive impairments remains unclear. Reports from animal studies on chemotherapy associated brain dysfunctions indicate that chemobrain might be a results of a number of intertwined molecular and genetic factors such as: increased permeability of blood – brain barrier (BBB), altered activity of plasma membrane pumps within central nervous system (CNS), DNA damage, telomere shortening, dysfunction of

cytokine secretion, impaired neuronal regeneration and oxidative stress [9,10]. Some studies also indicate that chemobrain might result from a combination of vascular (vascular lesions, anemia) and immune deficiencies (increased inflammation at the injection site, severe immune response) as well as altered expression of apo-lipoprotein E gene, involved in the development of Alzheimer’s disease [11].

### Discussion

Recent studies on patients treated with different chemotherapeutics shed some light on possible mechanisms of chemotherapy associated cognitive impairments. For example, it has been shown that doxorubicin, a common drug for a variety of different types of cancer, causes oxidative damage to neutrophil mitochondria likely contributing to the development of cognitive dysfunctions [9,12]. Furthermore, studies on neurotoxicity of 5-fluorouracil, one of the essential medicines listed by WHO, revealed that it reduces levels of BDNF (brain - derived neurotrophic factor) and double-cortin, a protein regulating neuronal migration in the brain, leading to the development of chemobrain [13]. Fortunately, in majority of cases chemotherapy triggered cognitive dysfunctions are not permanent, disappearing within weeks at best and months at worst after the treatment.

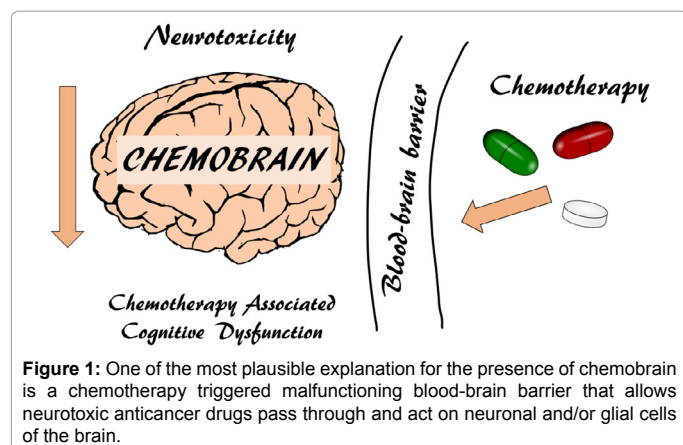
So far, no effective prevention method against chemobrain is available, however over years several successful pharmacological and non-pharmacological medical interventions aimed at treating

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chemotherapy associated cognitive dysfunctions have been made. The most common pharmacological interventions involves administration of psychostimulant drugs such as methylphenidate, used in Attention Deficit Hyperactivity Disorder (ADHD) treatment while the most prevalent non-pharmacological intervention involves cognitive – behavioral therapy [6,14]. The therapy aims to identify and comprehend patient's problem in relation to his/her thoughts, emotions and behavior focusing on "here and now", not dwelling with the past [15].

### Blood-brain barrier as a likely factor in the chemobrain development

The concept of blood-brain barrier (BBB) was first introduced by a nineteenth century German neurologist, Max Lewandowsky and further developed by Paul Ehrlich, a Noble Prize winner and precursor of the use of what we call now modern chemotherapy. Recent studies show that BBB might be the most important factor in the pathogenesis of chemobrain, either preventing it or contributing to its development [16,17] Figure 1.

BBB is a key cellular boundary protecting brain against unwanted, harmful cytostatics from the blood during chemotherapy. Due to its physical and biochemical properties, BBB almost uniformly prevents chemotherapeutics from entering sensitive brain tissue – a disadvantage in brain cancer treatments, but a significant benefit in all other types of cancer therapy effectively protecting brain against chemotherapy induced neurotoxicity. BBB permeability is determined by the unique structure of the capillary endothelium allowing only for transcellular diffusion (small molecules, nutrients and fat soluble substances) or carrier facilitated active transport of regulatory proteins and hormones. In addition to its morphological, brain capillary endothelium acts also as a biochemical regulator, actively metabolizing certain regulatory molecules such as adrenaline or dopamine as well as some metabolites and toxins whose activity would otherwise disrupt homeostasis and affect brain function [18,19].

Studies show however that BBB, though highly efficient, might be prone to damage in some metabolic or autoimmune diseases and certain types of metastasizing, cancers making it possible for harmful molecules to enter the brain causing neuronal dysfunction and cognitive impairment. It might be hypothesized that in case of chemobrain, certain neurotoxic chemotherapeutics alter BBB functionality and morphology, allowing them to enter CNS and disrupt homeostasis affecting neuronal function and contributing to the development of chemotherapy associated cognitive impairments [16,17].

### Chemobrain: Nature and treatment – A light in a tunnel

Chemobrain is a set of cognitive dysfunctions of unclear etiology and undetermined incidence diagnosed in cancer patients. It is considered to be a side effect of chemotherapy however evidence suggests that some cancer patients experience cognitive dysfunctions prior to the initiation of chemotherapy treatment indicating that other, chemotherapy independent, mechanisms might be involved. It is possible that observed changes result from a combination of various, unrelated factors such as: previous surgery, effects of anesthesia, hormonal therapy, menopause, anxiety and depression, chronic fatigue syndrome, comorbidities, adverse reactions to drugs used in adjunctive therapy paraneoplastic syndromes or genetic predisposition [2]. The number of possible contributors to the pathogenesis of chemobrain calls for a better, more appropriate name for this condition i.e., cancer therapy associated cognitive changes.

### Conclusion and Further Studies

So far, there have been no prospective studies addressing this condition. The lack of knowledge, information and appropriate diagnostic and monitoring tools is particularly detrimental for an elderly patient (>65 years) population, more susceptible to troublesome and life quality affecting cognitive dysfunctions. In the absence of effective preventive methods, raising awareness and educating patients about possible cognitive dysfunctions as a result of chemotherapy should be implemented. All cancer patients undergoing treatment and experiencing cognitive dysfunctions should be informed about the transient nature of the dysfunction and given options of either pharmacological or cognitive – behavioral therapy aimed at reducing the symptoms.

Recent studies on cancer medication and drug development have tremendously improved methodology and safety resulting in a reduced number of side effects and neurotoxicity. With improved drug development protocols we may expect better ways of preventing and controlling symptoms of chemobrain.

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