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ORIGINAL ARTICLE

The impact of cancer treatment on cognitive efficiency Chemobrain – does it exist?

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Abstract
Background and objectives: Cognitive function deficits are considered the most significant symptom in the course of many mental and somatic diseases. The aim of this work is to assess the intensity of cognitive deficits in patients diagnosed with lung cancer, treated using antineoplastic chemotherapy. An attempt has also been made to link the applied treatment methods with the intensification of cognitive deficits.
Methods: 68 people were qualified to take part in the experiment. The subjects were divided into two groups: the affected with diagnosed lung cancer and healthy subjects from the comparative group. The evaluation of cognitive functioning was conducted using the following neuropsychological methods: the Trail Making Test A & B (TMT), the Stroop Color-Word Interference Test, and the Verbal Fluency Test (VFT).
Results: The treated subjects with a diagnosed malignant disease during the first stage of treatment recorded significantly worse results of the tests used to evaluate cognitive efficiency than the comparative group during each task. The hypothesis regarding statistically significant differences in the cognitive functioning between subsequent examination stages in the group of patients with cancer was not confirmed.

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Conclusions: (1) In the people diagnosed with a malignant disease, subject to chemotherapy, it was possible to observe significant deterioration of cognitive efficiency in the scope of information processing speed, working memory, executive functions and verbal fluency. (2) No statistically significant differences in cognitive functioning were found between subsequent stages of the examination.

Introduction

Cognitive function deficits are considered the most significant symptom in the course of many mental and somatic diseases.[1] Increasingly more attention has been paid in recent years to cognitive function disorders in the people subject to antineoplastic chemotherapy. The interest in cancer treatment neurotoxicity as well as the general impact of a malignant disease on the function of the nervous system served as a foundation for many studies aimed at describing the phenomenon referred to as chemobrain or chemofog. Initially, this term was used to describe cognitive dysfunctions associated only with the application of chemotherapy.[2] However, cognitive disorders were also observed in cancer patients in whom other forms of treatment were applied (radiotherapy, hormonal therapy, surgical procedures or general anesthesia).[3] A new term, i.e. cancer-related cognitive dysfunction (CRCD), which has a broader meaning than chemobrain, has appeared in literature.[4]

Depending on source, the frequency of occurrence of the chemobrain phenomenon oscillates from 17% to 75%.[5] Difficulties in precise determination of the scale of this disorder presumably results from methodological differences described in the scientific papers published so far (examined group, applied methods of cognitive functioning assessment, type of cancer treatment). What is interesting is that cognitive deficits occur even before chemotherapy is applied in nearly 1/3 of cancer patients. The potential explanations for that include among others an influence of emotional factors associated with the very diagnosis of a chronic and life-threatening disease, i.e. malignant disease.[6,7]

Deteriorated cognitive function was described mainly in the group of patients with breast cancer.[8] Research studies present information regarding the occurrence of this phenomenon also in the people suffering from lung cancer, testicular cancer, prostate cancer, in the group of patients with head and neck cancer, with lymphoma, multiple myeloma, in patients after hematopoietic cell transplantation, as well as in patients with the carcinoid syndrome.[5]

Cognitive disorders – as a consequence of cancer treatment – are characterized by lesions classified to the so-called Mild Cognitive Impairment group (MCI).[3] Research studies regarding cognitive dysfunctions in patients treated due to a malignant disease demonstrate reduced efficiency of mental processes in the following scope: deterioration in memorizing and remembering, reduced switch of attention, poorer concentration, reduced psychomotor speed, decreased speed of visual analysis and synthesis.[9–11] It is said that cognitive deficits linked with chemobrain have a short-term nature in the majority of cancer patients. There were, however, cases during which such deficits were maintained for months or even years in a group of about 35% of the affected patients during disease remission.[12] Some studies indicate that cancer-related cognitive disorders may be long-lasting and occur even after 5–10 years after treatment.[13,14]

The aim of this paper is to assess the intensity of cognitive deficits in patients diagnosed with lung cancer, treated using antineoplastic chemotherapy. We formulated the hypothesis regarding the reduction of cognitive effectiveness in the group treated with anticancer chemotherapy compared to the control of healthy people (I) and about the deterioration of cognitive performance at subsequent stages of cancer therapy (II).

Methods

The procedure of selecting people to the experimental group was performed at random based on a draw. Sixty-eight people, aged 50–58 were qualified to participate in the experiment. The subjects were divided into two groups, i.e. the affected with diagnosed lung cancer (group A, $n = 32$) and healthy subjects from the comparative group (group B, $n = 36$).

All the patients and the subjects from the comparative group were native Poles from central Poland, not related to one another. The authors of this study did not interfere with the process of diagnosis or treatment at any stage of the study.

Type A

The patients hospitalized at the Department of Chemotherapy with the Sub-unit of Diagnostics and Oncological Therapy of the Regional Oncological Centre at the Voivodship Specialist Hospital in Lodz (Poland) were qualified for the experiment.

The following knock-out criteria were considered during the experiment: metastases to the central nervous system, completed palliative and elective radiotherapy of the central nervous system, diagnosis of axis I or II mental disorders (before commencement of cancer management), inflammatory or autoimmune disorders, central nervous system traumas, the level of intellectual functioning below average, overuse or addiction to psychoactive substances,

pharmacotherapy which may negatively affect cognitive efficiency (besides chemotherapy), and unwillingness to give informed consent. Prior to the start of the experiment, a case history was obtained from each patient using the standardized Composite International Diagnostic Interview (CIDI).[15,16] The evaluation was performed in each case by the same person - a clinical psychologist.

Qualification for participation in the study was carried out in each case by the same person

- An oncologist.

The examined patients were treated with medications from two groups:

- Cycle-specific agents which destroy mainly cells in the cellular cycle, but provide lower -effectiveness in relation to the G0 phase (cisplatin, carboplatin);

- Phase-specific agents which destroy cells in a particular cycle phase (antimetabolites: gemcitabine, pemetrexed; alkaloids: vinorelbine; taxoids: paclitaxel, docetaxel).[16]

Type B

The CG comprised healthy subjects without any familial cases of mental disorders. The group of healthy controls was composed of community volunteers who were qualified for the study based on the criteria of the psychiatric CIDI interview.[15] The individuals suffering from other psychiatric diseases, axis I and II disorders, neurological disorders, or diagnosed with substance abuse or dependence, were excluded from the experiment.

Cognitive functioning evaluation

The study was carried out using the following neuropsychological methods: the Trail Making Test A & B (TMT), the Stroop Color – Word Interference Test, and the Verbal Fluency Test (VFT). Detailed characteristics of the research methods applied were presented in the following paper: Talarowska et al.[18]

Based on the results of the tests conducted, the efficiency of the following cognitive functions was analyzed: information processing speed (TMT), working memory and executive functions (TMT, Stroop test), verbal fluency (VFT).

Survey procedure

The evaluation of cognitive functioning was performed in each case by the same person using the methods described previously (by a clinical psychologist, neuropsychologist).

The neuropsychological tests in group A were performed three times: on the day of inclusion in the experiment (stage I – before chemotherapy), 4 weeks later (stage II-after the first cycle of chemotherapy), 6 weeks later-after the second cycle of chemotherapy (stage III). The neuropsychological tests in group B were used once – on the day of qualification for the experiment.

There were 32 people in group A during stage I, 29 people at stage II, and 23 people at stage III. No reasons why individual subjects refused to take part in the subsequent stages of the examination were registered.

Statistical analysis

A statistical analysis of the material was performed with the use of both descriptive and inferential statistics. A two-tailed critical region was employed in the testing of the statistical hypothesis.

The qualitative characteristics of the groups of affected subjects and healthy controls were expressed as frequencies and shown as percentages. An arithmetical mean (M) was calculated in order to characterize the average values of quantitative features. Statistical dispersion measures included the values between the minimum and the maximum, and standard deviation (SD).

Distributions were measured with the use of the Shapiro–Wilk test. The following tests were applied in the comparison of nonparametric variables in the test groups: the Pearson $\chi 2$ for qualitative variables, the Wilcoxon signed-rank test for two related groups for quantitative variables, and the Mann–Whitney U test for two independent groups to determine the coincidence of distributions (for quantitative variables). A one-way analysis of variance (Levene's test modified by Shaffe) was used to compare results at successive stages of the experiment. Statistical significance was defined as $p < 0.05$[19] in all the analyses, which were conducted using STATISTICA PL, version 12.

Ethics

The individuals taking part in the experiment were chosen for the study group at random without replacement sampling. Participation in the study was voluntary; any personal data and results were kept confidential. Before making a decision to participate in the study, the subjects were informed of the purpose, assured of the voluntary character of the experiment and guaranteed that their personal data would be kept in secret. Written informed consent was given in accordance with the study protocol, approved by the Bioethical Committee of the Medical University of Lodz (No. RNN/497/13/KB).

Results

The social and demographic characteristics of the examined individuals and the information regarding the course of the disease are presented in Table 1.

The tests used to evaluate cognitive functioning in the examined groups

Table 2 presents average results of the tests used to evaluate cognitive functioning (Table 2) in the examined groups. Individuals from the comparative group were compared with the patients treated due to cancer at the first stage of the therapy. The treated patients diagnosed with a malignant disease recorded significantly lower results than the comparative group in each task (hypothesis I).

Table 3 presents results of the analysis of variance of the results recorded at each of the three stages of the examination in group A. The hypothesis regarding statistically

Table 1 Participants' demographic and clinical features.

	Group A M (SD)	Group B M (SD)	
N		32	36
Age (years)		59.08 (4.87)	54.57 (3.96)
Male / Female (%)		28 / 4 (76.0 / 24.0)	9 / 27 * (13.0/87.0)
Education (%)	Vocational	4 (12.5)	9 (25.0)
	Secondary	25 (78.0)	24 (67.0)
	Higher	3 (9.5)	3 (8.0)
Duration of disease (months)		2.55 (1.74)	–
Type of cancer treatment	C	30	–
	D	2	–

Group A, subjects with lung cancer; Group B, comparative group; C, cycle-specific cancer medications + phase-specific agents; D, phase-specific cancer medications; M, mean; SD, standard deviation; *, *p* statistically significant.

Table 2 Results of tests conducted in group A and in group B.

	Group A Stage I M (SD)	Group B M (SD)	Group A vs Group B
N	32	36	–
TMT A (seconds)	47.23 (20.39)	29.56 (9.41)	$p^* = 0.002$
TMT B (seconds)	115.06 (53.69)	57.83 (17.78)	$p^* < 0.001$
Stroop test RCNb (seconds)	33.64 (7.92)	23.06 (2.76)	$p^* < 0.001$
Stroop test NCWd (seconds)	76.39 (16.63)	56.81 (13.44)	$p^* < 0.001$
Änimals fluency test	17.78 (6.12)	23.44 (5.52)	$p^* = 0.026$
Letter k fluency test	11.75 (4.52)	17.21 (3.17)	$p^* < 0.001$
Sharp objects fluency test	9.11 (3.33)	11.69 (4.49)	$p^* = 0.013$

Group A, subjects with lung cancer; Group B, comparative group; TMT, Trail Making Test; M, mean; SD, standard deviation; *, *p* statistically significant.

Table 3 Results of tests conducted at subsequent stages of the examination in group A.

	Group A Stage I M (SD)	Group A Stage II M (SD)	Group A Stage III M (SD)
N	32	29	23
TMT A (seconds)	47.22 (20.39)	42.31 (14.96)	41.74 (17.83)
TMT B (seconds)	115.05 (53.68)	96.45 (44.17)	99.39 (33.33)
Stroop test RCNb (seconds)	33.64 (7.93)	34.41 (7.19)	38.82 (23.21)
Stroop test NCWd (seconds)	76.39 (16.63)	69.52 (15.72)	70.91 (26.95)
Fluency test semantic category	17.78 (16.12)	14.79 (3.53)	10.73 (4.77)
Fluency test semantic category	9.11 (3.32)	9.41 (3.67)	9.82 (3.63)
Fluency test letter category	11.75 (4.53)	12.14 (4.48)	11.52 (5.68)

Group A, subjects with lung cancer; Stage I, before chemotherapy; Stage II - 4 weeks later, after the first cycle of chemotherapy; Stage III - 6 weeks later, after the second cycle of chemotherapy; M, mean; SD, standard deviation; *, *p* statistically significant.

significant differences between subsequent stages of the examination was not confirmed (hypothesis II).

Discussion

The hypotheses presented in the introduction were confirmed only partially. The treated people diagnosed with a malignant disease recorded significantly lower results of the tests aimed to evaluate their cognitive efficiency than the comparative group in each task during the first stage of the experiment. The hypothesis regarding statistically significant differences in the cognitive functioning between subsequent examination stages in the group of patients with cancer was not confirmed. The size of the examined groups may be of importance at this point.

When analyzing the impact of chemotherapy, in particular the unwanted effects, in the patients suffering from cancer attention is mainly paid to a series of side effects regarding physical ailments such as a decline in production of blood cells, hair loss, constipation, nausea or vomiting, oral ulceration.[17] The mental aspect of post-chemotherapy dysfunctions, i.e. deteriorated cognitive functions, has become the subject of studies only recently. As mentioned before, the frequency of occurrence of these disorders (chemobrain) oscillates between 17% and 75%.[20] These disorders usually have a mild and transient nature.[3] They affect working memory effectiveness, verbal and visual memory,

psychomotor speed, speech fluency; they are additionally demonstrated in difficulties in the scope of visuospatial functions and complex activity, concentration and attention disorders,[21] and varied capacity of short-term memory. As previous experiments indicate, it is hard to provide a clear list of all clinically significant disorders of cognitive functions after the use of chemotherapy. This is caused by the disproportion between the subjective ''chemobrain experience'' by patients and the evaluation of its intensity in objective neuropsychiatric tests.[22]

Cognitive deficits may negatively affect patients' quality of life, hinder their professional work and various social functions. A malignant disease is beginning to become a chronic disease for an increasing number of patients subject to cancer management. In some patients treated additionally using the surgical method, a relapse of the disease will never take place or cancer will reveal itself again after many years.[22] Many people from this group return to full professional activity. Therefore, it is extremely important to gradually increase awareness and knowledge of the phenomenon of chemobrain.

The incidence of malignant neoplasms has almost doubled in the last three decades in Poland. There were more than 140,500 new cases in 2010 (approx. 70,000 men and 70,500 women). The most common cancers affecting men are lung cancer, which represents about 1/5 of all malignant diseases, followed by prostate cancer (13%), large intestine cancer (12%), and urinary bladder cancer (7%). The most common types of cancer among women are: breast cancer, which represents about 1/5 of all malignant disease, large intestine cancer (10%), and lung cancer (9%).

The mechanisms of formation of chemo-dependent cognitive disorders have not been thoroughly examined yet.[14,23] The factors determining the occurrence of the chemobrain phenomenon include: neurotoxic impact of cytostatic drugs, which is characterized by damage of neurons and surrounding cells, dysregulation of neuron repair processes, a change in the level of neurotransmitters,[24,25] oxidative stress, DNA damage, hormonal changes, autoimmune causes (increased level of proinflammatory cytokines), vascular lesions, genetic predispositions, as well as psychosocial factors.[24] The previously mentioned other forms of cancer treatment are also important, i.e. surgical treatment, radiotherapy, general anesthesia, or the action of supporting drugs in cancer management (antiemetic drugs, analgesic drugs). The very process of a malignant disease is also of significance (among others tumor location and pressure on surrounding tissues), coexisting diseases, and the patient's mental condition.[25]

Ahles et al. presented interesting studies. The authors described a relationship between the presence of E4 allele of apolipoprotein E (APOE) and cognitive disorders in patients treated due to breast cancer and lymphoma.[25] It was additionally demonstrated that people with COMT-Val genotype experience deterioration of cognitive functions after the application of supplementary chemotherapy more often.[26] Genetic polymorphism has an appreciable effect on the mechanism of action of cytokines, the mechanism of action of the blood-brain barrier, as well as the mechanism of DNA repair.[14] Genetic testing provides directions for further studies.

Chemotherapeutic agents have an ability to induce oxidative stress, hence increase synthesis of cytokines which may reach the central nervous system after passing through the blood-brain barrier.[27] The most important cytokine released in the plasma of the patients subject to chemotherapy is TNF alpha, whose negative impact on the central nervous system is revealed by means of oxidative damage of neurons.[28] One of the most popular chemotherapeutic agents – doxorubicin, influences the formation of peroxide free radicals in the plasma, which cause apolipoprotein A1 oxidation (APOA1). APOA1 potentiates TNF alpha synthesis affecting p55 and p75 receptors of the blood-brain barrier, which eventually leads to the initiation of the phenomenon of apoptosis, i.e. death of neurons, by this cytokine.[29] Many experiments show that the patients who were subject to the use of chemotherapeutic agents from the group of taxanes or anthracyclines demonstrated an increase in IFN-a, IL-1B, IL-6, IL-8, IL-10, MCP-1.[30,31] It was also demonstrated that the application of a standard dose of chemotherapy causes an increase in the level of cytokines: IL-6, IL-8, IL-10, TNF alpha, particularly in the patients who additionally experienced post-chemotherapy cognitive disorders.[32] In animal models, acetylation of H3 histones and reduced activity of DHAC deacetylase in the hippocampus may also be causes of the chemobrain phenomenon after the use of chemotherapeutic agents such as cyclophosphamide, methotrexate or 5-fluorouracil, which leads to a drop in the proliferation of hippocampal nervous cells.[33]

The chemobrain phenomenon is associated with overproduction of not only reactive oxygen species (ROS) but also with an increased number of reactive nitrogen species (RNS). Activated glial cells produce and release local cytokines, which is associated with increased synthesis of nitric oxide.[34,35] An increase in the production of reactive oxygen species and the oxidative stress linked with the path of changes of nitrogen oxide represent the most frequent causes of DNA damage in nervous cells.[36,37]

It is assumed that some patients may be genetically predisposed to the occurrence of the chemobrain phenomenon. A research study conducted in children diagnosed with acute lymphoblastic leukemia suggests that cognitive function disorders, as a consequence of oxidative stress in the course of chemotherapy, are associated with the polymorphism of three genes of oxidative stress, i.e. the SLCO2A1 variant of G allele and the GSTP1 variant of the allele, NOS3 894T.[38]

The majority of chemotherapeutic agents induce oxidative stress in a malignant tissue; this action affects also the brain and other organs. Morphological changes of the brain tissue, i.e. irregularities of density and immaturity of dendritic spins caused by oxidative stress in the course of cyclophosphamide application, may serve as an example.[39] Besides the attempts to seek a molecular ground for the chemobrain phenomenon, studies based on the neuroimaging technique were carried out, mainly using MRI and PET-CT. These studies indicate that there is a relationship between a completed chemotherapy and structural and functional changes, most of all in the frontal cortex, the white matter, which correlate with the deficit in cognitive functions.

Psychological factors are yet another important factor in the formation of cognitive dysfunctions in cancer patients. The appearance of problems with memory and attention concentration may take place even before chemotherapy

commencement.[6] This is the so-called nocebo effect, i.e. a situation where the occurrence of symptoms or their intensification depends on the negative attitude towards the planned therapeutic procedure. Other factors having an impact on the occurrence of cognitive deficits may be stress, anxiety, depressive disorders or fatigue. Both physical and mental stress may lead to an increase in the level of circulating cytokines. It was demonstrated that the presence of acute or chronic stressors leads to an increase of among others IL-6 and IFN alpha.[40] Co-occurrence of memory disorders and fatigue was described as a result of the action of TNF alpha cytokine in female patients subject to chemotherapy.[41] A change in the activity of the immune system is also one of the pathomechanisms present in both a malignant disease and depression.[42]

Owing to the complexity and prevalence of the chemobrain phenomenon, seeking further relationships between cognitive function deficits in patients with cancer and the applied chemotherapy seems to be a necessity.

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Conflicts of interest

The authors have no conflict of interest to declare.

Limitations

The limitation of the presented results is the size of the studied groups, as well as the disproportions in the demographic distribution of study participants in each of them (gender).

The authors of the work are aware of these limitations.

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