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NEUROCOGNITIVE CHANGES IN CANCER PATIENTS AS A CURRENT CHALLENGE IN PSYCHO-ONCOLOGY
NEUROKOGNITIVNE PROMENE KOD ONKOLOŠKIH PACIJENATA KAO AKTUELNI IZAZOV U PSIHOONKOLOGIJI

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Summary
Introduction. Along with a high intensity emotional distress, cancer patients often face neurocognitive changes that are particularly pronounced after chemotherapy. Clinical features of neurocognitive deficits in non-central nervous system cancer patients. So far, studies have demonstrated that neurocognitive changes most often occur in domains of executive functions, attention and concentration, working memory, information processing speed and visuospatial abilities, but there is still no definite protocol for the diagnosis and management of this condition. Potential causal mechanisms and risk factors. Apart from chemotherapy, there are other factors associated with the development and manifestation of neurocognitive deficits in cancer patients: genetic, biological, psychological and socio-demographic. Assessment of cancer-related cognitive impairments. When assessing potential cognitive impairments, it is beneficial to combine neuropsychological test battery and self-report questionnaires for the assessment of cognitive and affective status, as well as modern neuroimaging methods that will indicate neural (structural and functional) changes underlying neurocognitive deficit. The role of psychosocial factors: implications for future research. In addition to cognitive reserve and emotional status, the patient’s personal characteristics may very likely play an important role in explaining neurocognitive functioning and neurocognitive adaptation of cancer patients upon completion of treatment. Conclusion. Further studies are needed to elucidate the mechanisms underlying neurocognitive changes in cancer patients, with special emphasis on the contribution of psychosocial factors. Based on the novel findings, adequate and timely cognitive rehabilitation treatment will be provided for patients suffering from malignant diseases. Key words: Neurocognitive Disorders; Cancer Survivors; Psycho-Oncology; Neuropsychology; Neuroimaging; Cognitive Dysfunction; Affective Symptoms; Chemotherapy-Related Cognitive Impairment; Psychological Distress; Personality

Sažetak
Uvod. Uz visok intenzitet emocionalnog distresa, onkološki pacijenti često se suočavaju sa neurokognitivnim promenama koje postaju naročito izražene nakon hemoterapije. Kliničke manifestacije neurokognitivnog deficita kod pacijenata koji nemaju tumor centralnog nervnog sistema. Dosadašnje studije su pokazale da se kognitivne smetnje najčešće javljaju u domenima egzekutivnih funkcija, pažnje i koncentracije, radne memoriije, brzine procesiranja informacija i vizuospacialnih sposobnosti, te za iste još uvek ne postoji krajnje definisan protokol dijagnostike i lečenja. Potencijalni etiološki mehanizmi i faktori rizika. Pored hemoterapije, važnu ulogu u nastanku i manifestaciji neurokognitivnog deficita kod onkoloških pacijenata imaju i drugi: genetski, biološki, psihološki i sociodemografski faktori. Metode procene neurokognitivnog deficita kod onkoloških pacijenata. Za procenu eventualnog neurokognitivnog oštećenja najbolje je koristiti kombinaciju koja uključuje neuropsihološku dijagnostiku i inventare za samo procenu kognitivnog i afektivnog statusa, kao i savremene metode neuroimizđinj dijagnostike koje će ukazati na neuralne (strukturalne i funkcionalne) promene koje leže u osnovi neurokognitivnog deficita. Uloga psihosocijalnih faktora - smernice za buduća istraživanja. Pored kognitivne rezerve i afektivnog statusa, potencijalnu ulogu u objašnjenju neurokognitivnog funkcionisanja i neuropsychologoje adaptacije po završenom lečenju vrlo verovatno mogu imati i karakteristike ličnosti obolelih. Zaključak. Neophodne su nove studije koje će omogućiti dalje rasvjetljavanje mehanizama koji leže u osnovi neurokognitivnih promena kod onkoloških pacijenata, sa posebnim akcentom na doprinos psihosocijalnih faktora, a na osnovu kojih će dalje biti omogućen i adekvatan i pravovremeni kognitivno-rehabilitacioni tretman obolelih od malignih bolesti. Ključne reči: neurokognitivni poremećaji; onkološki bolesnici; psihonkognitivna dijagnostika; neuroimizđing; kognitivni poremećaji; afektivni simptomi; kognitivni poremećaji uzrokovani hemoterapijom; psihološki poremećaji; ličnost

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Introduction

Emotional distress, anxiety, depression and adjustment disorders have long been recognized as significant psychological concomitants of malignant diseases, but recently the attention of clinicians and researchers has also been drawn to cognitive impairment in cancer patients. The phenomenon known as “chemobrain” was noted by systematic studies focusing on side effects caused by different cytostatic drugs and it includes a sense of mental fatigue and other cognitive changes reported by those suffering from malignant diseases. Studies have demonstrated that not only can difficulties in cognitive functioning occur during and directly after chemotherapy, but can also be present before the beginning of treatment, but also for years after cancer treatment ends [1, 2]. The onset of neurocognitive deficits, although mainly provoked by cytostatic agents affecting the central nervous system (CNS), appears to be influenced by other factors as well; this has resulted in recent introduction of the term cancer-related cognitive impairment (CRCI) used for this phenomenon [3]. Furthermore, as these neurocognitive changes are often subtle in intensity, their recognition requires more complex diagnostics, which makes it difficult not only to determine their etiology and mechanisms of manifestation, but also developing suitable therapeutic approaches. Although many questions in this area remain open, neuroscience with its interdisciplinary approach is certainly making a significant progress in elucidating different aspects of this phenomenon.

Clinical features of neurocognitive deficits in non-central nervous system cancer patients

Previous studies have shown that cognitive impairment most often occurs in the domain of executive functions, attention and concentration, memory, and information processing speed [1–3]. The data on the incidence of cognitive deficits in cancer patients vary from one-third to more than one-half, depending on methodological aspects of the respective studies [4]. The CRCI has most frequently been investigated in patients suffering from breast cancer, but research shows that cognitive changes may occur in patients with other non-CNS cancers as well, i.e. testicular, gynecologic, prostate, colorectal cancer, non-Hodgkin’s and Hodgkin’s lymphoma [3, 4]. Despite the fact that cognitive difficulties are most pronounced directly after completion of chemotherapy [1], mild cognitive problems may persist for years. In comparison with patients treated only with local therapy, breast cancer and lymphoma survivors treated with systemic chemotherapy scored significantly lower in the domains of verbal memory and psychomotor functioning even ten years after completing the treatment [4]. Also, in some survivors, cognitive difficulties manifest as a subjective sense of impaired cognitive functioning, which does not necessarily correlate with cognitive achievement on neuropsychological tests which remain the same, or with affective symptoms often associated with cognitive difficulties. A possible explanation for this discrepancy is that the perceived cognitive difficulties, despite good results on neuropsychological tests, may be a consequence of neurofunctional disturbances that follow brain damage due to treatment [5]. Neurocognitive deficit, especially when pronounced, along with impaired memory, manifests in the form of planning and decision making difficulties, problems in organization, difficulties in acquiring new skills, or with multitasking; problems with finding the appropriate word or naming objects, but also with emotion regulation deficits. Today, many patients return to work after completing treatment and their cognitive difficulties become more evident in the context of heightened demands with a potential of provoking additional psychosocial distress. Many cancer survivors report cognitive impairments being burdensome for years, affecting their self-confidence and social relationships, forcing them to use compensatory strategies in adjusting to work requirements [3]. It is undeniable that intact cognitive functions are extremely important for the quality of life of cancer patients and treatment outcome. More recent studies suggest that cognitive impairment not only affects adherence but also the course and outcome of malignant disease, since it increases the risk of mortality in older patients up to six times [6]. Unfortunately, there are still no well-defined protocols for prevention and treatment of neurocognitive deficits in cancer patients. The up-to-date research findings point to the benefits of physical activity, cognitive-behavioral therapy and cognitive rehabilitation, while neurostimulating, neuroprotectant and antineuroinflammatory therapeutic agents, along with some antidepressants and antide-mentia drugs, are still in the testing phase [3]. This implies that the timely and adequate detection of potential neurocognitive deficits is of crucial importance in the treatment of cancer patients and should be included in clinical protocols.

Potential causal mechanisms and risk factors

Although passing of chemotherapy through the hematoencephalic barrier was earlier thought to be impossible, today it is assumed that even a low concentration of many cytostatic agents, especially platinum-based chemotherapy, can penetrate the blood-brain barrier (BBB) and thus lead to damage of the neural progenitor cells and oligodendrocytes, as well as hippocampal neurons [5, 7]. Apart from these direct effects, neurocognitive deficits in oncology patients can be provoked by indirect mech-
anisms such as metabolic and hormonal changes brought on by treatment, by activation of inflammatory cytokines, genetic polymorphism, fatigue and other bodily damage, as well as certain psychological factors [3]. Negative impact on cognitive functions seems to be most frequently realized through proinflammatory mediators and cytokines (e.g. tumor necrosis alpha, interleukin-6). One of the hypothesis is that by entering the brain peripheral proinflammatory mediators and cytokines stimulate glial cells to release central cytokines, which in turn cause local neuronal injury resulting in different cognitive symptoms [8]. Furthermore, not only does chemotherapy seem to take effect through cytokines that compromise the metabolism of key neurotransmitters involved in the regulation of sleep, learning, memory and mood (e.g. noradrenaline, serotonin and dopamine) [9], but a similar effect, although not as intense, can be caused by the tumor itself alongside different treatment modalities and processes, psychological and emotional distress, that all provoke systemic inflammation and compromise the immune system during a malignant disease [8]. Also, elevated oxidative stress, i.e. oxygen free radicals that are released during cytostatic therapy, can lead to deoxyribonucleic acid (DNA) damage in neurons, and the oxidative damage of DNA can be associated with lower levels of cognitive functioning and lower frontal lobe gray matter density, as well as poorer functional magnetic resonance imaging (fMRI) activity for years after completion of chemotherapy treatment [10]. Hormonal therapy used in the treatment of breast cancer in patients with estrogen positive receptors, which acts through blocking and lowering hormonal levels, is also linked to poorer cognitive functioning, since, among its other effects, it can lead to the reduction of cholinergic activity, decrease the serotonin receptors’ activity and most probably accelerate the cell aging process due to the antioxidant effect of estrogen [11], while one of the mechanisms that explains the development of CRCI is exactly accelerated aging. Among the predisposing factors for CRCI, there are also findings about the apolipoprotein E gene ε4 (ApoE4) that codes catechol-O-methyltransferase (COMT), and the brain-derived neurotrophic factor (BDNF) involved in neural reparation and long-term potentiation. Studies aimed at establishing the importance of these genes in the etiology of CRCI have shown that breast cancer and lymphoma survivors with at least one ε4 allele score significantly lower in domains of visual memory and spatial abilities, as well as in the domain of psychomotor functioning, compared to persons who are not carriers of this allele [12]. Compared to COMT Met carriers, COMT Val carriers score lower on tests assessing attention, verbal fluency and motor speed [13], while carriers of the BDNF Met allele are more resilient to CRCI, especially in the domain of verbal fluency and multitasking ability [14]. The patients’ age and cognitive reserve capacity are factors that contribute to their cognitive achievement, in the way that older patients and those with lower education levels score significantly lower on neuropsychological tests after the completion of chemotherapy treatment, e.g. have poorer results on information processing speed [15]. Etiologic factors for the occurrence of cognitive deficit in patients seem to vary, i.e. different patients are vulnerable to different mechanisms [9], making the approach to this phenomenon even more complex.

**The assessment of cancer-related cognitive impairment**

As there is still no general agreement on the affected cognitive domains and underlying neural changes, and due to the discrepancy that is sometimes registered between subjective and objective measures, in the process of diagnosing CRCI it is best to use a combination of neuropsychological assessment, self-reports, and neuroimaging whenever possible.

**Neuropsychological assessment**

According to the International Cognition and Cancer Task Force, a neuropsychological battery of tests is the "gold standard" for the assessment of CRCI [16]. Although there is still no standardized test battery for the assessment of this phenomenon, in order to achieve more research cohesion, authors recommend using tests aimed at assessing key cognitive domains in which the impairment is registered: e.g. Hopkins Verbal Learning Test-Revised for verbal learning and memory, Controlled Oral Word Association Test, or the Multilingual Aphasias Examination for speeded lexical fluency and Trail Making Test for processing speed, out of which the last two also cover some aspects of executive function, with a recommendation to use additional tests for the assessment of working memory [16]. Other instruments that can be used in assessing CRCI include Mini-Mental State Examination, Montreal Cognitive Assessment Scale, Rey Auditory Verbal Learning Test, Rey Complex Figure Test, selected subtests from the Wechsler Memory Scale, and The Wisconsin Card Sorting Test [2, 6, 17]. Due to the many methodological limitations of cross-sectional studies, it is recommended to use a longitudinal design with mandatory baseline cognitive assessments prior to chemotherapy [16], since up to one third of patients may manifest a cognitive deficit even before starting the treatment [1]. Moreover, each neuropsychological assessment must include an assessment of affective status, especially when it comes to cancer patients, whose diagnosis and demanding treatment, already carries a high prevalence of psychological distress, which can affect their cognitive functions as well [18–21]. There are a number of instruments appropriate for this purpose, e.g. the Depression, Anxiety and Stress Scales, Positive and Negative Affect Schedule, Beck Depression Inventory-II, Beck Anxiety Inventory, and Spielberger’s State-Trait Anxiety Inventory [1, 20, 21]. Fatigue and sociodemographic factors should also be taken into account for the neurocognitive assessment, especially if we consider the fact that
the elderly population, along with CRCI, is at a higher risk for other neurodegenerative processes [22].

**Self-report assessment**

Self-report questionnaires provide insight into how patients perceive their problem and how they function in everyday situations. The discrepancy registered between the achievement on a neuropsychological battery of tests and self-report instruments is often linked to mood changes, but quite possibly also with compensatory strategies patients use when confronted with cognitive demands [9]. This is probably even more pronounced in individuals with a higher cognitive reserve, since they are presumed to be more capable of activating alternative neural networks, thus succeeding to function as before in spite of significant structural damage [23], although with a subjective sense of putting in more cognitive effort. The most frequently used instruments include Functional Assessment of Cancer Therapy - Cognitive Function and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [3], more precisely the cognitive functioning subscale of this questionnaire, which assesses cognitive aspects of the quality of life. Additionally, the Behavior Rating Inventory of Executive Function - Adult Version, as one of the more ecologically valid complementary instrument for assessing behavioral aspects of executive functions [24], can be applied when performing a more complex examination [17,21].

**Neuroimaging assessment and findings**

The most valuable data on structural and functional changes and mechanisms that are the core feature of the patients’ neurocognitive deficits come from neuroimaging studies. However, the potentials of multimodal magnetic resonance imaging in defining the exact pathophysiology and underlying biological mechanisms are not yet fully exploited. The fMRI has shown that chemotherapy, particularly anthracycline-based therapy compared to non-anthracycline protocols, is the risk factor for cognitive deficits in patients with breast cancer. The affected brain areas include the left precuneus connections with the frontal, hippocampal, and lateral parietal regions, and on the neurocognitive level, they are primarily reflected in verbal memory impairment (immediate and delayed recall) [25]. Also, this method identifies reduced activity in brain areas responsible for the executive deficits which is most often seen in cancer patients after chemotherapy treatment, e.g. decreased activity of the dorsolateral prefrontal cortex, as well as significantly lower functional connectivity of anterior cingulate cortex [26]. Furthermore, negative effects of chemotherapy on executive function networks that support higher level cognition can persist for years upon completion of treatment [26]. This is also supported by findings obtained by voxel-based morphometry that point to significantly reduced grey matter volume in the left middle frontal gyrus and the left superior frontal gyrus in patients treated with chemotherapy, which is followed by self-reported difficulties in executive functions, primarily in the domain of initiation [27]. Some studies have found a reduced hippocampal volume in patients treated with chemotherapy, which is linked to poorer ability to access episodic autobiographical memories [28]. Along with the reduced grey matter volume in different regions, diffusion tensor imaging in breast cancer patients treated by chemotherapy also registered alterations in white matter microstructure, e.g. significant increases in mean diffusivity and radial diffusivity in the genu of the corpus callosum, decreased fractional anisotropy values in corpus callosum, frontal, parietal, and occipital white matter tracts, and a larger decline in white matter integrity in the right superior longitudinal fasciculus and corticospinal tract, which is followed by significant difficulties in cognitive and physical functioning, as well as disturbances in the domain of attention and verbal memory [29]. Magnetic resonance spectroscopy results, although rare, have thus far pointed to lower levels of N-acetyl aspartate in deep white matter of the left cerebral hemisphere in breast cancer patients treated with high-dose chemotherapy [30], lower N-acetyl-aspartate/creatinine ratio [31] and lower N-acetyl-aspartate and choline and N-acetyl-aspartate and myo-inositol ratios in breast cancer patients treated with chemotherapy [32]. Increased myo-inositol and choline, with decreased levels of N-acetyl-aspartate in the prefrontal cortex have been linked to subjective memory difficulties, but not to perceived difficulties in executive functions [32]. Although it is still unclear to what extent structural and functional brain changes are reversible, the persistence of some despite the later improved neurocognitive functioning, suggests a significant role of brain plasticity in alleviating the possible negative effects of chemotherapy on cognition [5].

**The role of psychological and social factors: implications for future research**

**Cognitive reserve and cognition**

The fact that the neurotoxic effects of chemotherapy and the malignant disease and its treatment in general, will not have the same intensity on all patients’ cognitive functions, speaks in favor of the existence of factors that increase the risk and make the patients more vulnerable to negative side-effects of the illness and treatment, while other factors may act protectively. We have already described some of these factors, and what remains to be elaborated further is the role and the importance of cognitive reserve on the patients’ neurocognitive functioning. The concept of cognitive reserve can explain the frequent discrepancy between brain damage and its clinical manifestation, i.e. cognitive reserve is an individual’s ability to efficiently use the existing neural networks in response to cognitive demands even in case of brain injury [23]. The brain is thought to have combat strategies to overcome the injury by using either the existing approach to cognitive information processing or by developing novel compensatory strategies. This implies that the individuals with
higher cognitive reserve capacity, which can be restored throughout the course of life (including a wealth of intellectual and occupational activities and knowledge acquired during life), are more apt in dealing with brain damage compared to those with a lower cognitive reserve [23]. This is also supported by studies that demonstrate that in dealing with age-related brain pathology or Alzheimer’s disease, individuals with a higher cognitive reserve remain without visible symptoms much longer than those with a low cognitive reserve, who manifest the symptoms at an earlier stage [33]. Likewise, patients with breast cancer and lower cognitive reserve prior to treatment, upon its completion manifest more difficulties in the domain of information processing and executive functions [15, 34]. A single proxy or a combination of proxies are often used for measuring the construct, which primarily includes variables of socio-economic status such as education level and occupation, but also cognitively stimulating activities that summarize one’s experience. The premorbid intelligence quotient is also a commonly used proxy [23, 33]. It is suggested that socioeconomic status affects brain development and cognition, through different prenatal factors, quality of parental care and intensity of cognitive stimulation, which all later reflects differences in language processing and executive functions (particularly in the domains of working memory and inhibitory control), but differences can also be seen in emotional processing [35]. Physical activity has been found to be a significant protective factor of cognitive functioning in cancer patients treated with chemotherapy as well, e.g. patients who increased their physical activities showed significant improvement in cognitive health [17]. Lately, there is a tendency to design and apply an all encompassing questionnaire that would cover all the complexity of this construct; however, due to the existing methodological and measurement challenges, the authors who systematically studied the quality of the existing questionnaire for assessment of cognitive reserve agreed that a final recommendation for one specific questionnaire cannot be made [36].

**Personality, stress, anxiety, depression and cognition**

Emotional distress and mood disorders are well known psychological factors that affect cognitive functions, and these have to be controlled during neuropsychological assessment, while the importance of other factors, including the personality, remains insufficiently explored up to date. Studies so far have demonstrated that intense and chronic stress, as well as increased cortisol level associated with stress, weaken prefrontal networks and contribute to hippocampal volume reduction and decrease neurogenesis in adults, so it is a risk factor for difficulties in higher-level cognitive processes and executive function [37, 38]. Anxiety resulting from insufficient control of intrusive thoughts intensifies a person’s focus on negative stimuli and affects executive functions, especially working memory [39], while depression is linked to deficits in executive function, memory, attention and concentration [40]. Long lasting psychological distress is generally associated with cognitive deterioration and increases the risk for the development of dementia [41]. The psycho-oncology research findings indicate that compared to non-chemotherapy patients, chemotherapy patients have higher levels of stress, anxiety and depression as well as more neurocognitive disturbances associated with them [21, 42]. Emotional distress associated with CRCI or its intensification, have been registered, for instance, in the domains of verbal memory and concentration, speed of information processing and executive functions [42]. Preliminary results of our study that combined neuropsychological assessment and magnetic resonance neuroimaging, point to the atrophy of nucleus accumbens following chemotherapy treatment in breast cancer patients [43], which can be linked to the previously registered affective state but also to deficits in the domain of executive functions which are significantly associated with the intensity of patients’ emotional distress [21]. Since basic personality dimensions are strong determinants of behavioral, emotional and cognitive patterns and since they generally affect one’s lifestyle, personal interests and health related behaviors [44], i.e. adaptation to cancer and its treatment [45], and considering the common neural substrates of certain aspects of personality and cognitive functions [46], we believe that they can be important factors of vulnerability, but also the factors of resilience, in the context of neurocognitive adaptation of cancer patients, thus significantly contributing to the cognitive reserve. The most recent studies indicate that high neuroticism, i.e. increased tendency toward experiencing distress and low conscientiousness, i.e. poorer organizational abilities and tendency toward less disciplined and responsible behavior, are strongly associated with cognitive health and increased risk for mild cognitive impairment and dementia [47, 48]. Also, openness to experience, characterized by intellectual curiosity and eagerness to search for new and different experiences, which strengthens one’s cognitive reserve through numerous cognitive activities, has proven to be a factor of resilience to cognitive decline in older adulthood [49]. The findings from our study support the importance of personality traits for neurocognitive functioning of cancer patients, point to a significant correlations between high neuroticism and difficulties in the domain of behavioral regulation, and between low conscientiousness and difficulties in the domain of metacognition in breast cancer patients prior to chemotherapy treatment [50]. We also found increased vulnerability for manifestation of executive function deficits in patients with a high negative affectivity as a personality trait [21]. Certainly, these findings require further longitudinal research.

**Conclusion**

As demonstrated, cancer-related cognitive impairment is a phenomenon with multiple clinical aspects. However, the answers to numerous questions
on the etiology and mechanisms that predispose someone to develop and manifest it are still lacking. Along with factors associated with the malignant disease and its treatment, biological and genetic factors, as well as specific socio-demographic characteristics, the question on the significance of psychological factors as determinants of both vulnerability and resilience to neurocognitive deficits after chemotherapy treatment still remain open. Since the most effective strategy for preventing and treating neurocognitive deficits in cancer patients is still in research phase, shedding light on the role of psychological factors would contribute not only to prevention and timely recognition of neurocognitive deficits in the most vulnerable patients, but also to the development and implementation of different cognitive-behavioral interventions and cognitive rehabilitation programs with the aim of improving neurocognitive functioning and quality of life of cancer patients. Taking this into account, intense collaboration of neuro-radiology and clinical psychology specialists is needed to clarify the etiological mechanisms and possible treatment for cancer-related cognitive impairment, by correlating findings obtained by modern neuroimaging methods and neuropsychological diagnostics. A cooperation with all other specialists involved in the diagnostics, treatment, and rehabilitation of cancer patients is also required.

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